# CLINICAL SCIENCE

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## ILLUSTRATED BY PERSONAL EXPERIENCES

BY

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*BY THE SAME AUTHOR*

"Clinical Disorders of the Heart Beat."

"Clinical Electrocardiography."

"The Mechanism and Graphic Registration of the Heart Beat."

"Lectures on the Heart."

"The Soldier's Heart and the Effort Syndrome."

"Blood Vessels of the Human Skin and their Responses."

"Diseases of the Heart described for Practitioners and Students."

# PREFACE

This book has been written in the hope of encouraging some young men, whom curiosity impels, to contemplate Clinical Science as a field of fruitful and interesting life work. Clinical Science should lead the medical sciences of the future as it has led them in the past, and it can do so by maintaining full consciousness of its powers and responsibilities. In many directions physiology and animal pathology are fundamental to human pathology; Clinical Science, which includes human pathology, is fundamental to the proper pursuit of the healing arts. Because of its immediate and constant bearing upon the health of the people it is the most responsible of the medical sciences, and has direct powers of which its auxiliaries can very rarely become possessed. But if it is to take its rightful place in our community, it must possess full opportunities, and must be conducted with purity of motive and rigid adherence to truth. There are some questions concerning the elucidation of disease and its processes in man, which are among the hardest that human intelligence and endeavour has to answer; there are abundant problems requiring merely sound method and perseverance for their solution. Clinical Science requires for the study of its chief problems, and for the guidance of those engaged upon its lesser problems, men of first-rate ability, who will enter this field, not only to work and to encourage and help others in working, but to foster their science, watching the direction and character of work and building up and guarding the privileges of workers.

The opening chapter of this book outlines the scope of Clinical Science, attempting to impress the paramount importance of this member of the family of medical sciences, and deals generally with directions of work and with method. The remaining chapters chiefly contain brief descriptions of, and appropriate comments

upon, a series of researches inspired by contacts with patients. The problems that I have studied in the last 25 years have begun, almost without exception, in this way, though in choosing illustrations for this book, only those more directly related to bedside work have been included. A clinical worker starting to enquire into the meaning of some phenomenon exhibited by a patient, is often led into work of a purely physiological kind ; such work as that which helped to isolate the pacemaker of the heart, or traced out the normal path of excitation wave in auricle and ventricle, or studied the constitution of the normal electrocardiogram, though inspired by, and indirectly very relevant to, clinical problems, does not properly belong to Clinical Science. The illustrations comprised in these chapters are deliberately confined to work upon which I have personally been engaged. It is true that by extending, or by confining, the illustrations to the work of others, far more dramatic and important results could have been included. The method here adopted restricts the field of illustration and leaves much unillustrated. But such work as is described is not without variety ; and there is the very weighty advantage that the book becomes a record of personal experience, describing from intimate knowledge the development of work and the ideas relating to method, which have come during that work's progress. The book may be considered not as a treatise on Clinical Science and its method, but rather as containing material, which some day a worker and thinker more competent for the greater task may perhaps use.

In writing the chapters, I have endeavoured truthfully to set down the manner in which the chief problems in Clinical Science upon which I have worked were prompted, with the fortunate accidents of observation, and the lines of reasoning, which led to progress and eventually to conclusion. It will be found that many of these researches started in some simple and isolated observation, which aroused interest. I have never felt urged to set out in deliberate search for cure or for the discovery of some undescribed disease. It has been my faith that the normal advance of Clinical Science comes by pressing unceasingly against the whole line of defence, rather than in mass attacks on strongholds ; that the surest way is to search continuously for vulnerable points, to sap and break in a little

here and there, and to consolidate everything, however small, that seems insecurely held. Thus every small patch of new territory won becomes a permanent gain, and takes an essential part in the gradual disintegration of the defence. Exceptionally there are notable incidents, but most forward progress is achieved by innumerable small steps, and the larger steps always result from less conspicuous ones. Time and again it happens that, when one worker is arriving at a conclusion, it is reached almost simultaneously by another. Problems are solved when the time is ripe. The process of inconspicuous disintegration leads sometimes to a more obvious breach in the line of defence. But the capture of the vantage points is sooner or later inevitable and may happen from one or more directions. Some in breaking through a small defence will find, by good fortune more than by design, a vantage point undefended ; the very few will see this point from a greater distance, but it has been brought into their view by the work of others. The important thing to realise is that, when it is coming near, it will be reached, if not by the leap of genius, then by the more gradual process in which all who work soundly can help. It is often said, and it breeds discouragement, that the problems of Clinical Science are exceptionally difficult. This is not so of most. There are abundant problems of every grade from simplicity to complexity ; and the difficulty of the next problems to be solved in this field is governed, not by the nature of the work, but by the ability of those who have worked previously. If they would, many in this country might be working continuously and successfully in Clinical Science.

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Thomas Lewis.

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# CHAPTER 1.

## THE SCOPE AND METHODS OF CLINICAL SCIENCE.

### CLINICAL SCIENCE AND ITS SCOPE.

The aim of all medical science is to combat suffering, to prolong life, and to keep mankind so far as possible in a state of vigorous health. Many branches of medical science have developed to this end but the parent stem from which they all sprang and to which they all still look for support and nourishment is the branch of medical science dealing with living human beings. Knowledge that is to become useful to the health of mankind almost always comes by a series of steps, the first of which is the recognition of the human need, the last of which is a test applied directly to the human problem. It is in the very nature of things that the study of disease, to be effective, must begin as it must end with disease itself, and that all knowledge applicable to human disease must owe its inspiration, directly or indirectly, to intimate contact with disease as this exists in living man. The parent science, so described from its fertility, might be called "experimental medicine" if this term had not come to convey too strongly the idea of experiment on animals. It would be called "clinical pathology" if the latter were not now narrowly fenced off by test tube and needle. It will be termed "clinical science."

This science in its widest outlook seeks first by observation and otherwise to discriminate between diseases as these occur in man; it attempts to understand these diseases and their manifestations; it seeks the cause of disease and studies its natural history; it attempts to cure or to prevent disease; when it cannot cure it endeavours to alleviate suffering. These

are the objects of the science; the manner of its work may be stated differently.

Knowledge requisite to the practice of medicine rests upon a tripod, the three limbs of which are each essential to the stability of the superstructure; these limbs are:—studies of living men in health and disease; studies of dead men; and correlated studies undertaken upon the lower animals. Clinical science in its work embraces all these three; but its central and unique province, most fundamental of all work pertaining to the practice of medicine, is that which concerns living men. This, however, cannot be divorced either from anatomy or from experimental work on animals without embarrassing all three, or without weakening the whole edifice. While many, and especially the more recondite, studies in morbid anatomy and in other branches of general pathology, and most studies in general physiology are properly undertaken by the corresponding branches of medical science, it is quite necessary to the proper progress of purely clinical study that these last should be most strongly linked with it. This linkage can be enduring only if clinical science retains its opportunities of studying both dead bodies and living animals.

It is essential that those who have held charge of patients and have studied phenomena in the living should themselves, and not through skilled deputies, explore the tissue changes that may underlie disturbed function; for while the skilled deputy may more accurately describe and name those changes in the tissues upon which he chances, he cannot enjoy either full opportunity or full inspiration to correlate function and structure. It is by this correlation that the meanings of many manifestations during life are explained; it is by correlation rather than by simple study of the cadaver that the meaning of illness and the cause of death are often or usually to be made clear.

It is essential that those who in studying human patients perceive opportunities for putting questions to the test of animal experimentation should themselves engage in such work; that correlation should not be left to the chance meeting and union of clinical and laboratory studies; that the spirit which moved the original inquiry should live, vitalising and directing the whole work in its progress along a broad path towards a practical goal.

To divide or attempt to divide medical research into ward research and laboratory research is narrow and harmful ; it is a profound error to believe that there is any essential difference in general method, however different may be the technique. The close union of the two maintains throughout the work both the full perspective of the central problem in its practical bearings, and the inspiration that should drive to its solution. It is just this integration that is of so much consequence to the vitality of medical research ; and this integration is, and always must remain, chiefly within the province of clinical science. He who can see the source of the problem, who can appreciate the fittingness of its final solution, is uniquely fitted to guide the whole train of thought and of enquiry.

From the standpoint of work the legitimate scope of clinical science may be claimed as follows. Work belonging to it exclusively is any such relating to the identification of disease, to its cause, mechanism, diagnosis or management, which is undertaken upon man himself. Human physiology is also definitely—though not exclusively—within its province, for healthy men form controls, which students of disease must use. Clinical science has also the long established right to wander unimpeded into any branch of medical science in search of information directly relevant to the problems of human disease. These excursions into animal physiology, pharmacology, and into all branches of general pathology, are not only legitimate, they are also quite necessary. They are necessary to establish the linkage that is so strong a source of mutual inspiration. They are required to win information that otherwise would not be forthcoming ; for the worker in the allied science is rarely so aware of the precise need of clinical science as is the worker in this field. But the worker in clinical science must restrain himself from the temptation to stray often or far, remembering that there are many to study thoroughly the problems of physiology and pathology and few to study similarly those of disease in the living man.

In science, curiosity is the seed, criticism regulates the growth and trains the plant to its final form. Scientific work can be conducted only by a rigid adherence to truth, which takes no heed of consequence, but seeks knowledge for its own sake.

In the daily work of observation, experiment, and thought, there is the continual effort to discriminate between what is true, less true, and false. These are standards appropriate to scientific work in general. They are equally appropriate and necessary to clinical science. But clinical science is unusually placed in respects that call for special consideration.

## FOUNDATION OF CLINICAL BELIEF.

It behoves every worker to examine closely the foundation upon which he sets out to build. In research that directly concerns patients conclusion bases itself upon information derived from three sources, namely, from the recorded observations of others, from what is told by patients, and from personal observation.

A worker in physiology can often start from the records left by previous workers; in medicine this procedure is more precarious. This is so for several reasons. In its early development, medicine, like chemistry, was grossly contaminated by superstition and by dogma; chemistry has cleansed itself; but medicine remaining as it does in intimate contact with the fears and hopes of countless sick people and with the motives and reactions of those who surround these sick, is unable quickly to win freedom. Those who record facts and views relating to patients, have not been, and are not, chosen, like those who make science a career, for their ability to observe with originality, to think critically, and to express themselves precisely. Inaccuracies in statement of fact are difficult to detect, when observations cannot be repeated under conditions that are known to be sufficiently similar. For these reasons past records, which we to-day are compelled to use as a basis for further thought, contain many more pitfalls for the unwary reader than by comparison do contemporary records in other sciences. There is as yet little general appreciation of the degree to which past records are misguiding us by misstatement of fact, by unjustifiable inference, and by dogmatic utterance. A very grave defect is the dearth of systematic statements of evidence, and the over-emphasis of hypothesis. Past records cannot be taken at their face value with impunity; they must be read and sorted out with close criticism. A special guard must be kept against the easy

acceptance of a diagnosis, however definitely this may be expressed ; judgment should base itself exclusively, unless the writer's capacity is beyond dispute and the diagnosis simple, upon actual evidence presented. It is wise to accept few or no statements of fact that have not been confirmed by abundant repetition upon different patients by different observers, to the point that the statement has come to receive general assent. It is unwise to accept any written inference or conclusion except upon unequivocal records of published evidence. Those who are critically familiar with them will realise how hardly this standard bears upon past writings, and how great and important from this standpoint becomes the task of revising current beliefs in every branch of clinical work. It is an unavoidable task, for upon its extent and thoroughness the rate of future progress will largely depend.

A second and important source of evidence is the patient's statement. No isolated statement should be accepted as vital evidence for any conclusion. Unanimous or frequent statements by different patients, if unprompted, may be accepted sometimes. Many intelligent patients make in all good faith statements about themselves that are quite untrue. Patients describe symptoms most accurately when cross-examined during their actual experience, and will frequently correct themselves or add valuable information when their attention is directed to specific points. In dealing with subjective phenomena, the personal experience of a trained observer is invaluable ; if the investigator can safely induce in himself the symptoms under study then he should do so.

Reliable evidence should come from the investigator's own observation of spontaneous happenings and from the result of his experiments. The observational method, most fruitful as it has been in the past and even in recent times, must through the mere process of exhaustion become less prolific ; the experimental method wherever it has been applied in the biological sciences has been found to open up new channels of progress. Consequently, progress in medicine is becoming less and less due to observing what chances to happen in beds filled by the routine demands of the unselected sick, and more and more attributable to intensive study of selected cases in which manifestations are deliberately sought or actually provoked.

The chief directions in which the observational and experimental methods are used will be outlined presently in this chapter; both methods will be illustrated freely in the chapters of this book; but the experimental method will be most freely displayed, not only because it is the least understood, but because it has now become the most certain way to progress.

## SANCTIONS FOR EXPERIMENTAL INTERFERENCE.

From the nature of its problems clinical science to be fertile must be experimental. It will be obvious, however, to thoughtful people, that experimental research upon disease may come from time to time into conflict with the welfare of the individual sick. When such conflict threatens, it is unquestionably right that research should give way unhesitatingly; any other system would be intolerable. Interference giving temporary discomfort, the patient willingly co-operating, is permissible; but interference calculated to bring risk, however slight, to a patient's health is unjustifiable. There are many simple experimental procedures now undertaken daily in testing patients, such as the temporary arrest of bloodflow to a limb, or puncture of the lobe of an ear, that are so trivial in effect and so little discomforting, that a simple warning of purpose is enough, the patient having opportunity to demur if he so chooses. The nature and purpose of the less trivial venupuncture should be explained and it is considerate first to ask permission. Arterial puncture is an interference less easy to justify; repeated puncture should be discountenanced. Nothing should be done to a sick person, which the investigator would not himself permit in similar circumstances to be done to himself or to his wife or child. The use of new remedies, calculated from other evidence to offer some prospect of benefit, and to be at the least innocuous; the withholding of a beneficial drug over a control period, in a case without urgency, to display more clearly its effects when given later; the provocation of a frequently recurring symptom, so that the precise circumstances in which it arises may become known; all these are clearly permissible under sanction, for they throw light upon the patient's own sickness and in general increase the prospect of its successful management.

## DIRECTIONS OF INVESTIGATION.

Work in clinical science takes one of two directions. It consists in studying diseases as diseases, or it interests itself in some particular manifestation of disease, a symptom or other phenomenon, which several diseases may have in common.

## STUDIES OF DISEASE.

*Discrimination and definition of states of disease.* When we speak of the discovery of disease, we use a phrase standing for the first clear description of what comes to be regarded as a specific disease, or state of disease. This work of discrimination is comparable to the isolation of specific biological species and is intended to serve a similar primary purpose, namely, to enable the same state subsequently to be identified by independent workers. Studies relating to the cause and mechanism of disease, to its natural history, and to its management can scarcely begin until this first step of discrimination has been accomplished. Recognition of a specific state originally based itself upon close resemblances between manifestations of ill-health in separate people, with or without the additional evidence of a common morbid lesion. At first such discovery was a matter of simple observation ; but it has become less simple as the common and more obvious descriptions of disease have been written, and the number of those still to be recognised has correspondingly diminished. While requiring freshness of sight and mind, so that the opportunity may be seized when it occurs, nevertheless progressive work of this kind has been and must continue to be a matter largely of good fortune, as when several patients of one type present themselves for examination in quick succession. To-day work along these lines cannot be a planned investigation ; it has become incidental to the routine of medical practice. There may be many forms of disease yet to describe, but it is manifest that most diseases of simple types have been named. There is work still to do in recognising the less obvious types. Moreover, there is very important new work to do, if one may express the matter a little differently but more clearly, in *defining* conditions of disease. To define, which is no more than to name at length and accurately, is quite fundamental to many studies that must be undertaken in the future ; and definitions of disease have as

yet hardly been attempted. Working towards precise definitions, and ultimately from them, is both instructive and prolific ; it leads to the belief that diseases are named much too often upon a simple, and perhaps loose, grouping of symptoms, that closer analysis of mechanism is necessary, and that this will lead in the future to much revision of terms. Definitions cannot be made satisfactorily in terms of grouped symptoms ; definition brings us quickly to intimate questions of causation. When we are brought, as we inevitably are, to these, then, as the history of medicine abundantly illustrates, it is found on the one hand that distinct diseases have superficial resemblances bringing them to be confused, and on the other hand that conditions previously thought to be unconnected have a common pathological basis. Instances of both kinds of reshuffling have been frequent and will no doubt often occur again. As our understanding of disease is incomplete, so, and in that measure, our classification remains artificial and lacking in finality. There are, in fact, few clear-cut discoveries relating to the mechanism of disease, which do not call for some changes of nomenclature. Changes of nomenclature shift the boundaries between what are regarded as diseases ; and the moving of a boundary at once requires us to revise our ideas of what is bounded. For example, when it became clearly proved that anginal pain often arises from coronary thrombosis, it was necessary to separate these cases out from "angina pectoris" ; and because angina pectoris thus acquired closer set boundaries, our ideas of this malady began at once to change, and they changed conspicuously. While the progress of nomenclature directly and importantly affects investigation of mechanism, likewise the latter often affects the former. There is an interplay between the two ; they should move forward together. In investigation the nomenclature of disease, until based firmly on cause, should usually be regarded as unstable. Briefly, there are two points to realise. Firstly, that the useful nomenclature of disease is becoming less a matter of simple and casual observation, and more and more dependent upon a close understanding of the mechanism of disease, and therefore upon concentrated and intensive study. Secondly, that the attempt to reach accuracy of definition is itself a strong stimulus and powerful guide to investigational work.

The manner in which the description and naming of disease may affect investigational work, and the purposes of attempting to define accurately, are illustrated in Chapters 13 and 14.

*Questions of causation.* The relation between cause and effect is a matter of common scientific interest ; but it is of unusual importance to the clinical investigator owing to his preoccupation with problems concerning the origin of disease and its manifestations.

When we enquire into the cause of a disease, we are often brought to consider a long chain of relevant circumstances, each circumstance in this chain inevitably leading to the next. Somewhere, however, in the chain there is a particular event, which is of cardinal importance to the individual, since it may be said to have set the chain of events in motion in him. There is an unfavourable reaction of the man to his environment ; in the case of a given disease it may result from an inborn defect of the individual ; in the case of another disease it may come from an encounter with abnormal environment. When we consider what we shall term the cause of a given disease in the individual, it is this circumstance to which we turn.

But questions of cause and effect cannot always be regarded simply from the standpoint of pathogeny, for there are different though equally correct practical aspects. The reason for diarrhœa in a given patient might be said to be an ulcerated gut, and we might be led on to the sequential statement that the ulcers have resulted from infection of a susceptible subject by the bacillus typhosus, and that the introduction of the organism came through water contaminated by the inadvertence of a typhoid carrier. The statement has gone far enough to illustrate. It would serve little purpose to discuss purely abstractly where in the whole chain of circumstance we should halt and point to cause. Knowledge is complete when the whole sequence of events has been explored ; but, if we are practical, we shall state the cause to suit the particular purpose we have in mind in seeking it. From the standpoint of the patient's management we may usefully halt at the ulcerated gut and the presence of typhoid fever ; from that of pathogeny we shall halt at the original infection of the subject ; and from that of public health we shall go back to the contaminated water and even to the carrier.

If we were to confine the term disease to specific and closely defined conditions, then we should recognise for each disease its equally definite pathogenic cause. But as long as diseases are undefined, so long shall we be forced to looseness in assigning cause. In this direction it must be confessed that medicine is often regrettably slipshod, as when many and diverse causes of one "disease" are enumerated under "etiological" headings. The words "caused by," as they are often used in such connection have no different meaning than the words "associated with," for we are in doubt if *a* causes *b*, *b* causes *a*, or *a* and *b* both result from a given set of circumstances; one of these three relations would necessarily hold, if the association were invariable.

A frequent source of confusion is that what is dealt with is not a disease but some particular manifestation of disease. Such a manifestation may seemingly arise in distinct sets of circumstance. If it is asked what is the cause of pathological dilatation of the heart? The reply might be in the form of such a list as:—obstruction of the aortic orifice, coronary thrombosis, pernicious anæmia, diphtheria. The list may form an aid to empirical diagnosis, but the philosophical unsoundness of the statement is marked by its patent failure to convey the strict and whole truth. First the list is incomplete and cannot usefully be made comprehensive; secondly, the statement fails to convey that in each and all of these states dilatation may not occur. In such a case the attempt to discover a common factor and to express this in clear language, often clarifies thought and may form the starting point of real progress. In the instances given we may formulate the cause in a deliberate phrase such as "inability of a well-supplied heart properly to discharge its blood content"; this statement sets out to become philosophical and, as it is brought nearer to perfection, its value to rational thought and to investigation increases. Their inclusion in one phrase brings the factors of causation into proper perspective, and it becomes evident that inability to discharge contents may result from increased resistance at the outlet or from decreased power of the heart's muscle to expel. But such statements, if they are to hold good, require for their construction close consideration of the malady from many angles. It is this consideration, and the reasoning involved with it, which open up new points of view and often lead to new and fruitful

enquiries. Incidentally it may be remarked that the final statement approaches in this instance closely to a definition; for dilatation is equivalent to retention of abnormally large blood content; the very fact is an assurance that the statement of immediate causation is soundly built. An illustration of investigation usefully following these lines is given in Chapter 6.

Speaking generally of diseases, there is no special method of investigating causation; knowledge may be derived from one of many sources. The disease may prove to be hereditary; it may be acquired. Cause may become revealed after a characteristic group of symptoms is seen to be associated with some definite morbid change; though the morbid lesions themselves are almost always secondary to a deeper lying cause. The disease may be found to result from a specific bacterium or protozoon, from a fault in diet, from exposure to a poisonous environment, or from a chain of varied circumstances. Causation has far more aspects than can be dealt with in this chapter. But one point of view is peculiarly relevant to clinical science. Although it is manifest that crucial information may come from bacteriological, protozoological, dietetic, or epidemiological study, it is also manifest that such studies depend for success upon relevant clinical discoveries. The cause of human disease never has been, and never can be, found purely within the walls of a laboratory; there must be at least some association, direct or indirect, with patients. This association has grown, especially in the case of bacteriology, to be too loose; it is quite necessary to the proper study of many diseases that the association should develop the intimacy that has proved so successful in investigation of tropical disease. The solution is not usually to be found by bringing men to work together as a team; but by the workers interested in a particular disease becoming sufficiently acquainted both with the clinical aspects of the problem and with that kind of special work, bacteriological or otherwise, most appropriate to the purpose. Lister was his own bacteriologist. It is necessary for other clinicians to follow this example, or for bacteriologists investigating human disease to control patients. An illustration indicating how usefully clinical, anatomatical, and bacteriological studies can be combined in exploring causation will be found in Chapter 12.

*Diagnosis, prognosis and treatment.* Clinical science studies individual diseases in three other directions all of which intimately concern the practical management of patients. These studies relate to diagnosis, prognosis and treatment.

Diagnosis in its early and crude state was based purely upon observation and its method of reasoning was empirical. It is becoming more experimental in its method, and now employs many different forms of tests; simultaneously its method of reasoning is becoming rational. Some remarks upon diagnosis from the standpoint of investigation and from that of its rationalisation will be found in Chapter 15.

Prognosis has been built and will continue to be built upon an observational basis; it bases itself upon experience. Many diseases are known to run short courses to death or to recovery; but there are many others, some acute and more chronic, in which the course is very variable. Knowledge of prognosis in these last instances is still very imperfect. There is before clinical science a great task in studying the courses of individual diseases and in formulating accurate and simple rules to aid the forecast of the patient's future activities and of his probable length of life. Accurately to collect the necessary information requires great care and infinite patience; and to draw from this information useful conclusions often involves critical judgment. These matters are dealt with at greater length and illustrated in Chapter 16.

Therapeutics is essentially an experimental science, and will always have experiment upon man for its chief basis. This branch of clinical science links the latter with pharmacology, to the inspiration of both. Sometimes it is necessary for the work to be so closely co-ordinated that the clinical worker should become his own pharmacologist. While progressive changes in treatment are suggested by pharmacology, and old treatments are rationalised by this science, the proof or disproof of a remedy's value must rest finally on the tests in patients. There are remedies, the beneficial effects of which, when applied to appropriate patients, are so rapid and so obvious in altering the course of disease, or in relieving its symptoms, that they are universally acclaimed as sovereign remedies. There are, however, very many diseases, the course of which we are able to modify little if at all by treatment. There are very many therapeutic

measures in daily use for which there is no scientific sanction, that is to say, there is no means of judging from recorded evidence whether they are useful or not. Dogmatic utterances have proved untrustworthy, and an academic train of reasoning does not suffice; there is but one good reason why a remedy should continue to be used, namely, that it has been found to be of service; because this standpoint is empirical, it is none the less fully scientific. The chief goal of clinical science is to devise new and better means of treatment. The manner in which such problems may be approached is indicated in Chapter 17.

We have been dealing with methods in which the disease itself is the focal point of study; the isolation and recognition of entities, the enquiry into the cause, course, and treatment of disease. There are other important forms of investigation.

### STUDY OF SPECIAL MANIFESTATIONS OF DISEASES

A very profitable line of study is that which enquires into separate but various manifestations of disease, whether these are subjective or objective.

The study of subjective symptoms has a unique practical value in that it relates to manifestations directly affecting the patient's welfare; these manifestations of ill-health must be dealt with, whether we know the cause of the disease producing them or not. But the study of subjective symptoms and other phenomena has a much wider importance, because it frequently throws a flood of light upon the processes and nature of disease, leading up to closer definition, to more intimate understanding and even to the malady's cause. It was enquiry into the meaning of the symptom "palpitation" and to a closely related phenomenon common to many different diseases, namely, irregular heart action, which led to the volume of productive work upon the mechanism of the heart beat. And it is to be noted that that work comprised not only studies of the disordered heart beat, but of the normal heart beat as well. Since symptoms, using the word in its broad sense, may usually be regarded in terms of disturbed function, the study of symptoms necessitates very close consideration of the relevant mechanism of the body while this is working naturally. The study of symptoms,

therefore, is the branch of clinical science which links it most closely with physiology and stimulates physiology to many of its most important new ventures. For the study of symptoms, when productive, always expands the corresponding branch of physiology. It is a notable fact that, in beginning to study a symptom, physiological information sufficiently complete to form a proper basis for the analysis of that symptom is very rarely available; often it is meagre. It must be sought in part or in whole before the symptoms can be studied. These preliminary studies often fall to the clinician himself, for he realises the precise information required and the full importance of acquiring it. No one can work rationally upon the mechanism of symptoms who is not primarily a clinician, and who does not become in his chosen field a physiologist also. There is no branch of medicine, if we class disease anatomically, which does not profusely illustrate this fact. The work of neurologists and their fundamental contributions to our knowledge of the normal function of the central nervous system is no isolated instance, but it springs at once to the mind.

*Transient phenomena.* It is frequent for a patient to complain of some symptom, or for some phenomenon to be observed in him, that is not continuous, but transient. Such phenomena cannot be studied too closely. The transient phenomenon may consist originally of some relatively simple change, followed maybe by secondary disturbances. A notable example is the paroxysm of tachycardia, a sudden increase in the rate of the heart beat to perhaps double, or more than double, its origina l level. These paroxysms come and go and they allow us to study to perfection the effects of change in the rate of its beating upon the heart, normal or afflicted by disease. It is almost as though we were able to turn a rapid series of rhythmic shocks suddenly into the auricle and to study the result at will; but it is actually done for us in the unanæsthetised subject without disturbance of chest wall or other structure. Sometimes the effects are profound; within a brief period of the onset, the subject presents the full signs of heart failure with congestion; a few hours later he presents none, the heart often returning at once to its normal size at the end of an attack. In such cases the unique and recurring opportunity is presented of studying in its many aspects, the manner in which heart failure develops. It is perhaps the most important

experiment upon the heart that nature repeats before our eyes. You may study heart failure by comparing normal subjects with those who show failure. It is not the same thing ; it is the chance of minutely comparing the normal and abnormal states of circulation in one and the same subject that is so important ; here is the perfect control. You compare the one and the other state within a short time period ; you can repeat and check your observations or modify your method of observation.

*Provocation of symptoms.* Symptoms are often transient, occurring under particular conditions, which are related by the patient. From the standpoint of investigation it does not suffice to accept these statements ; the patient should come under observation while displaying the symptom. In instances where the symptom is transient and oft occurring, the subject may be asked to undertake such an act as ordinarily provokes the symptom. Advantages of this method of procedure are that it allows in some measure the objective confirmation of subjective phenomena, and that whatever is observed can be observed repeatedly. What is done can be done under carefully controlled conditions, with a view to discovering any phenomena that are simultaneously displayed by the patient, and how these associated manifestations and the symptom itself are changed by varying the conditions of observation. Many recent instances of productive work of this kind, enjoying as it does the full advantages of the experimental method, might be cited. The method is illustrated freely in this book, but especially in Chapters 10 and 11 ; it promises to develop into a fertile branch of clinical science ; for while giving us much closer understanding of disturbed mechanisms, it has the power to unveil essential features relative to the cause of the disease studied.

*Collective investigation.* In studying particular manifestations of disease the collective use of cases of different types is usually advantageous. A simple form is the investigation of all the circumstances in which some manifestation of disease appears, the primary purpose being to find in these an invariable factor of causation. The usefulness of such correlation has long been recognised, and an example of the method will be found with additional comments in the description of work on capillary pulsation in Chapter 6.

In other instances the collective use of cases allows the effects of some manifestation common to several diseases to be more accurately studied. Thus, if certain changes in the small arterioles, or in the size of the heart, are thought to be the result of continued high blood pressure, these changes should be found in all the different states of disease in which such high pressure prevails.

A further use of the collective method is occasionally possible, in that it may teach how a given phenomenon is affected by varying circumstances. This is given simple illustration in Chapter 9, in which the influence of different nerve lesions, mixed, sensory, and sympathetic, according to the separate cases chosen, are observed upon a given reaction in the skin; discriminating but systematic observation of this kind manifestly acquires much of the power of the experimental method.

### THE OPPORTUNITIES PRESENTED BY INJURY.

A very little thought brings us to realise the great amount of knowledge concerning the human body that has come, and has yet to come, to us through injuries, especially from wounds owing to their relative simplicity, or from surgical interference because of its precision. Early and late much of our knowledge of the immediate effects of injury, of hæmorrhage, of paralysis and so forth, much of our fundamental knowledge concerning the defences of the body, such as the clotting of blood and the reparative processes, is derived from this source; the triple response of the skin to injury described in Chapter 7 is a recent example. The deliberate injury or excision of certain human organs has played a conspicuous part in discovering their essentialness to life or otherwise, their functions, and the disturbances resulting from their loss. Injuries often afford special opportunities for investigation, by bringing relatively inaccessible structures within easy reach; the investigation by Surgeon William Beaumont of the interior of the stomach of a man through an aperture caused by wound, had a far-reaching influence upon the physiology of digestion, and remains the most notable of such examples. Injuries afford opportunities in these and a variety of other ways. An illustration, that of arteriovenous anastomosis, is described in Chapter 4, in which other instances are also noted.

Surgeons, if they would, could contribute heavily to clinical science. The special opportunities for observation presenting themselves during the progress of operations may be noted; they are not utilised as they might be. Such investigations as those concerning referred pain largely depend on this method, which, however, must remain purely incidental, and must always be conducted within strictly prudent bounds. Deliberate interference, other than trivial interference or interference undertaken wholly in the interest of the patient, is not to be contemplated. It is for this reason of humanity that we appeal to the lower animals, and on this question there is still something to be said.

### THE APPEAL TO LOWER ANIMALS.

The use of the lower animals for experiment is the chief, and rightly the most valued, method of the physiologist; it is equally indispensable to several branches of pathology and to pharmacology. But here the use of animals will be discussed from a very limited point of view, namely, its direct application to clinical science. A method of studying human disease, advocated since Claude Bernard's time, is first to reproduce such disease in a lower animal, and then to proceed to investigate it in that animal. In theory ideal, in practice this is rarely possible of full accomplishment. Strictly speaking, you cannot by cutting or tying reproduce any human disease other than one arising out of injury. It is possible to produce disease closely akin to that seen in man by introducing into animals the original agent of the human disease, bacterial or otherwise, or by withdrawing some essential from the diet; but, because the animal and its reactions are different, the disease is not accurately reproduced. The great value of animal experimentation in clinical science—putting on one side the indirect and great contributions of physiological and pathological experimentation—lies in a different direction. Disease destroys certain organs or interferes with the functions of certain structures, giving rise to specific manifestations; these manifestations of disease may often be reproduced in animals. If we can be sure of accurate reproduction then their meaning and consequences in man may often be elucidated by further study. If by some interference we can occasion high blood pressure in a dog, we

have not reproduced the disease "essential hypertension," and there may be no justification for supposing that the two states have anything in common beyond high pressure; we can learn much, however, of the effects of high blood pressure by this method. To entertain the belief that disease has been reproduced because one of its manifestations has been caused to appear is to fall into a not uncommon but serious fallacy. A little thought will show the full significance of this statement and will bring the supreme importance of clinical research into view. When we investigate clinically some disease, or some manifestation of it, we may be seriously handicapped by circumstance; but we are possessed of the certain knowledge that what we study is precisely what we set out to study. That is a tremendous asset. The complete assurance is unattainable in studying an artificial phenomenon.

The use of animal experimentation in the work of clinical science is illustrated in Chapters 2 and 3.

NOTE.—Much of the material of this chapter, which is in effect largely a general commentary upon the original observations and experiments described in the remainder of the book, has been incorporated in my Harveian Oration (*Brit. med. Journ.*, 1933, ii, p. 717); other parts of it are derived from articles published in the same journal in 1930, i, p. 479, and 1932, ii, p. 1046.

# CHAPTER 2.

## THE PROOF OF AURICULAR FIBRILLATION IN MAN.

### THE ORIGINAL CLINICAL OBSERVATIONS.

The knowledge that the human pulse may beat irregularly came to us from the remote past. But it was not until the last century was ending, that forms of irregular heart action began usefully to be differentiated. Before that time a series of purely descriptive names, pulsus intermittens, pulsus trigeminus, pulsus irregularis, and so forth, served to conceal the lack of precise and serviceable knowledge ; nothing was known of the mechanism of cardiac irregularities. Analysis of their mechanism, leading to modern understanding of these clinical arrhythmias, began with Arthur Cushny and was largely completed by Wenckebach and by Mackenzie. This analysis and the differentiation of types progressed together rationally, the latter being based on the results of the former. There are few instances within the range of medical knowledge that illustrate so remarkably and yet so simply the effects of differentiating types of disorder upon practical policies. When there was no appropriate differentiation, forms of cardiac irregularity were naturally confused with each other ; all were credited with the grave significance of the most serious ; they were treated alike and ineffectually. The very potent action of digitalis in what is the most frequent form of cardiac irregularity, here considered under the name auricular fibrillation, was still unrealised ; this meant that we were without any real understanding of one of the most valuable remedies for grave cardiac disease now known to us. The attempt to study irregular heart action as a whole inevitably and continually led to inaccuracies, contradictions, and disappointments. To state that final separation of human maladies into types is vital, sometimes to early and always to full progress,

may be belittled as a platitude. There is no harm in recognising the platitude for what it is, provided that recognition brings with it no sense of personal freedom from the fault of neglecting it. It is to be realised that none of us is thus immune; and only those are relatively immune who are constantly on guard, and who are fully conscious that the nomenclature of disease is highly unstable and know that the reason for this instability is change in our ideas of diseases as knowledge gradually grows. Neither lip service nor theoretical allegiance will avail; safety is to be in general won only by a constantly critical attitude and by periodic revisions as new facts come to discovery.

In distinguishing disorderly actions of the heart, among the first to be separated out and named were the simpler types now recognised as extrasystole, heart-block, respiratory arrhythmia; and here let us note, by way of emphasising what has gone before,

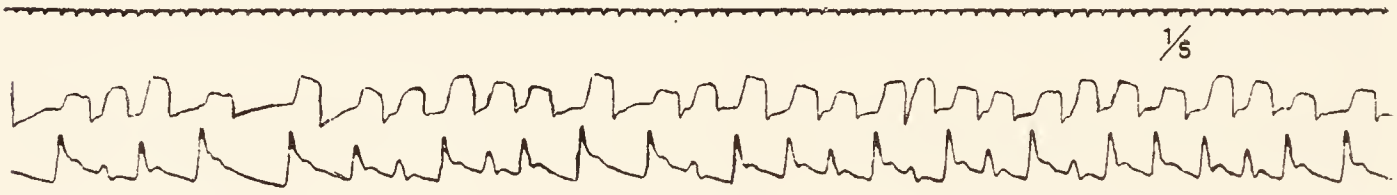


FIG. 1.—Simultaneous curves from the heart's impulse and the radial pulse illustrating gross irregularity of the heart's action.

that we cannot even yet be sure that these will all stand in a final classification. Gross irregularity, which would not fall into any of these groups, still awaited analysis. It is historically important to recognise that there was at first no adequate reason to suppose that gross irregularity was the invariable product of a given form of disturbance; it might comprise one or several types. But as countless curves were taken, so opinion began to form that most instances of gross irregularity are of a specific type. The view hardened as it was found that gross irregularity is essentially persistent, continuing unchanged from hour to hour, day to day, or even year to year, whereas other irregularities of action give place frequently to periods of undisturbed rhythmic action. It was this peculiarity which prompted the temporary name "pulsus irregularis perpetuus" (Hering) (Fig. 1). But what went farther in hardening the view into a conviction, was Mackenzie's discovery that gross irregularity and what he called the "ventricular form of venous

pulse " (Fig. 3), the venous pulse without auricular wave, seemed invariably to be associated. The conclusion that gross irregularity is a manifestation of a condition *sui generis* was reached very slowly and mainly through Mackenzie's laborious work; it did not find its full justification until very many electrocardiograms had been taken and these curves likewise came to be known as distinctive.

From the time when, in his efforts to analyse, Mackenzie singled out this disorder for special study, he took the view that the condition resulted from paralysis of the auricle (1902), for he could find no sign of its contraction either in pulsations recorded from the jugular veins or from the chest wall. This view for a time satisfied him and he believed that the disorderly rhythm arose anew in the ventricle. A few years passed, and his further work with patients changed this view. He noticed in cases dying of the disorder, that the auricular muscles might be hypertrophied, and with characteristic shrewdness realised that this could not be so if the auricle were indeed persistently inactive. He also found that rare cases of the disorder are paroxysmal, regular beating and with it normal action of the auricle being resumed. And so, with these additional facts in support, he launched and pressed (1904-1908) his striking hypothesis of " Nodal rhythm," in which the auricle was supposed to beat simultaneously with each irregular ventricular contraction. Thus he explained that the auricular contraction remains concealed.

This account relates in summary form the way in which the matter stood when I first became acquainted with James Mackenzie and his work in 1908, and like all those who then met him was forced to an interest in his great problem; for in those years the puzzle of this form of disorderly heart action and of its peculiar responsiveness to digitalis, which he had himself already discovered, dominated Mackenzie's thoughts. They were the years when his mind was at the height of its exceptional vigour and it was my privilege first as his disciple, and soon as his close friend, to listen long and often while he expounded the long history of his subject and told of his brilliant discoveries. Many long nights we spent together, to go over time and again the arguments for his and rival hypotheses, and in tedious searching and researching of intricate polygraphic curves, of

which he had so great a store. A year went by, time to become saturated with the arguments, and conversant with the last

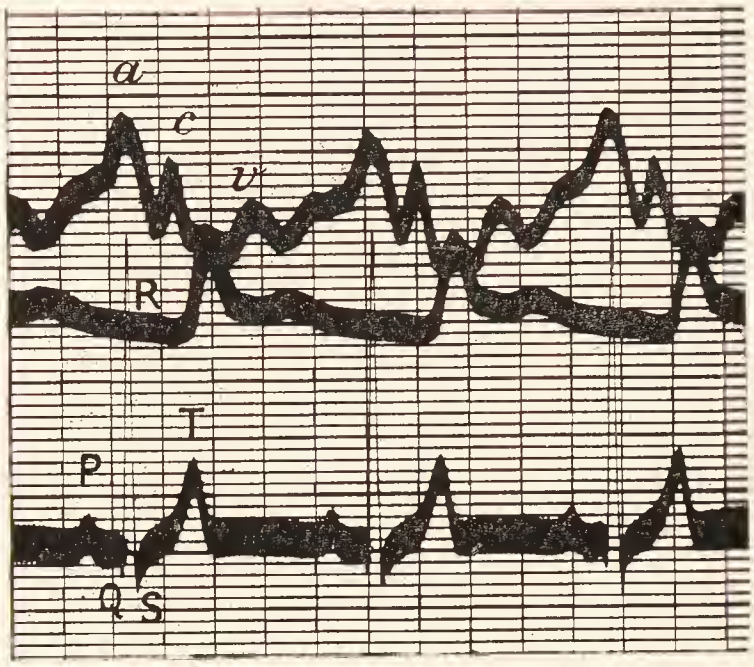


FIG. 2.—Venous, radial, and electrocardiographic curves from a normal subject. The vertical lines mark 1/5 sec. intervals ; and any line cuts the three curves at the same instant in time. The jugular curve consists of the auricular wave *a* and the two ventricular waves *c* and *v* : the electrocardiogram of auricular wave *P* and ventricular waves *Q*, *R*, *S* and *T*.

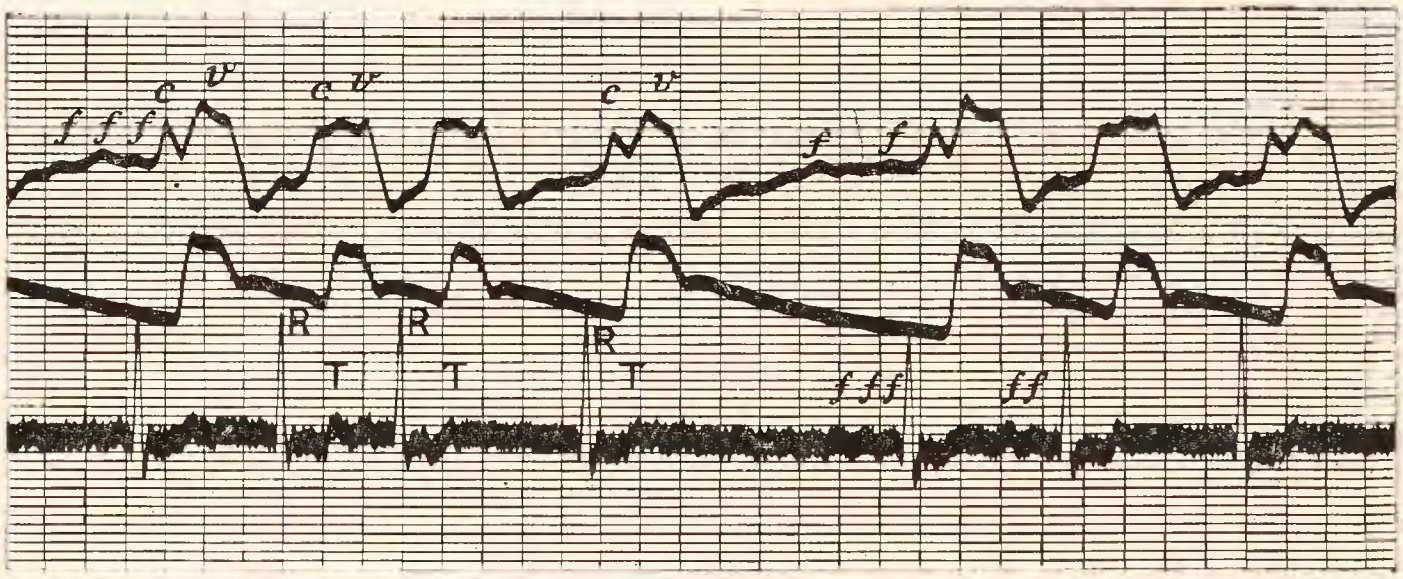


FIG. 3.—Similar curves from a case of auricular fibrillation. The heart's action is irregular. The jugular curve presents no *a* wave and the electrocardiogram no *P* wave, but both show oscillations, *ff*, transmitted from the fibrillating auricle.

details of relevant fact ; but there was no finality, no clinching proof. And then as chance directed there came an observation that changed fundamentally our direction of thought. It was in the earliest days of electrocardiography in this country, when a man came to my out-patient department suffering from paroxysmal tachycardia ; I won from him what in that year

was unique, namely, a complete series of venous and electrocardiographic curves, in and out of his attacks. These records gave a startlingly plain record of true nodal rhythm, or overlapping contraction of auricle and ventricle, producing high pointed venous waves, as the auricle was forced to pump blood back into the veins and not forward into the ventricles, and an electrocardiogram showing, like that of Fig. 4, invert *P* waves and shortened *P*-*R* intervals. The original records, unsuitable for reproduction here, were revealing, for the records of this tachycardia were altogether different from those of the disorder that had been under intensive study, and showed that this could not in fact be due to nodal rhythm. These records did more, for they were of regular tachycardia and thus sharply focussed attention on the weak point in Mackenzie's hypothesis, namely, its inability to explain *irregularity* of the ventricle; they drew the focus of attention away from the intricacies of jugular curves, where it had rested too long.

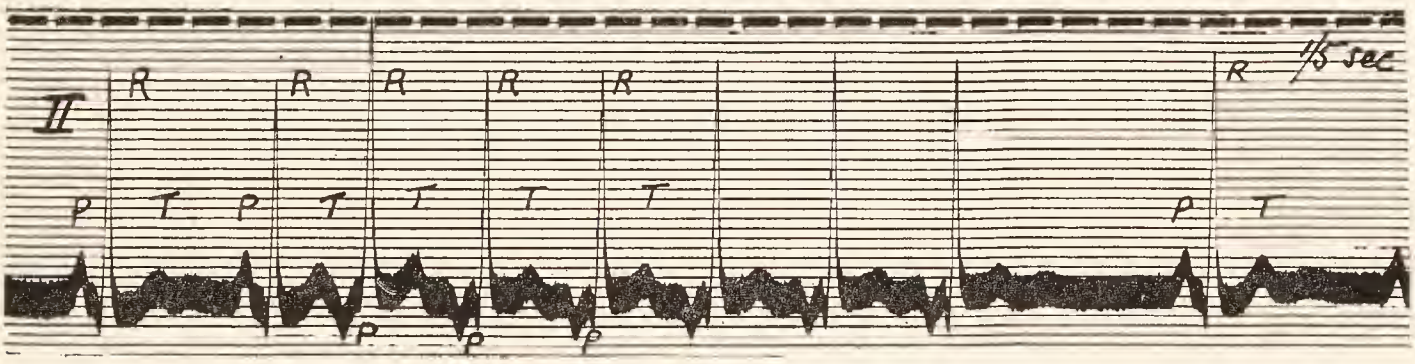


FIG. 4.—An electrocardiogram from a short paroxysm of *A*-*V* nodal origin (nodal rhythm). Two normal cycles are succeeded by six regular cycles of faster rhythm, marked by inversion of the auricular wave *P* and shortening of the conduction interval *P* to *R*. The return of normal rhythm is shown at the end of the record.

## ANIMAL EXPERIMENT; AURICULAR FIBRILLATION AS A CLINICAL CONCEPT.

Now in 1899 Cushny had drawn attention to the similarity between the arterial pulse curves of certain patients and those obtained when the dog's auricles are faradised. Although, as he said, he did not wish to assert the two conditions to be identical, the suggestion is there, and it was repeated in a similarly tentative form in a paper written later with Edmunds. This suggestion had been discussed many times by Mackenzie and myself, and both of us had talked of it with Cushny; but the evidence seemed so slight that the conclusion had not been

entertained seriously, I think, by any one of us. Nevertheless, it was remembrance of this paper, at a time when the need to explain the irregularity of the heart in the patient was urgent, which now led to the more careful examination of what was termed auricular fibrillation in animals, the term that had come to be used to describe the response of the auricles to a faradic current. When beating naturally all the muscle in the auricular walls shortens almost simultaneously, and the chamber diminishes much in size. This sharp, conspicuous, and rhythmic contraction of the auricle, immediately precedes that of the ventricle and in the dog is easily visible when the heart lies exposed. When the auricle is faradised it ceases to beat in this way ; there is no simultaneous and effective pull of its fibres ; the auricular wall stands almost still, but on its surface very rapid, minute, twitching or flickering movements are to be seen. The ventricle also changes its action, the responses become rapid and very irregular.

A curious illustration of how obtuse the mind can remain in failing to correlate facts within its knowledge is that for some time I had already possessed a series of electrocardiograms from patients exhibiting the disordered heart action and a second series from dogs in which the auricles had been thrown into disorderly action by faradisation. These then were ready, but had not been looked at side by side. Naturally it was not long before a searching comparison was made between arterial, venous, and electrocardiographic curves derived from patients and animals, and this brought together a striking show of evidence, some already known, some new, and much of it published almost simultaneously and independently by Rothberger and Winterberg, and forming as a whole a case going far towards carrying conviction. Briefly, this comparison displayed the following chief phenomena, common to the two disorders : an arterial pulse increased in rate and completely irregular ; a venous pulse of ventricular form, displaying no auricular waves but at times small rapid undulations in long diastoles ; electrocardiograms (Figs. 5 and 6) consisting firstly of irregularly placed ventricular complexes of supraventricular type, that is, such as were known to be associated with ventricular beats initiated as is normally the case by conduction from structures above ventricular level,*

* This form is variable, but is chiefly characterised by initial deflections (*R S or Q R S*) of brief duration as in Fig 2.

and secondly of characteristic rapid and irregular oscillations; in the electrocardiogram, as in the venous curve, there was no proper sign of auricular beat. But a mere list of points in common could hardly suffice, since things that are really different may simulate each other in many ways; and who can state how far correspondence must be traced to justify a conclusion of identity? More important from the standpoint of proof was the readiness with which auricular fibrillation explained

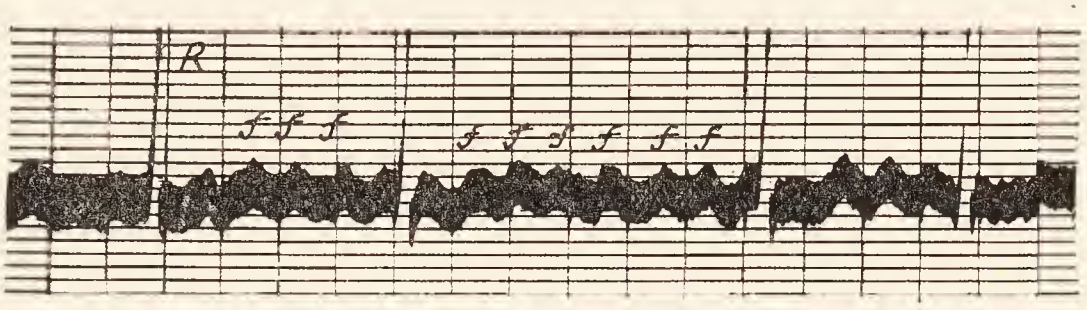


FIG. 5.—A human electrocardiogram from a case of auricular fibrillation.

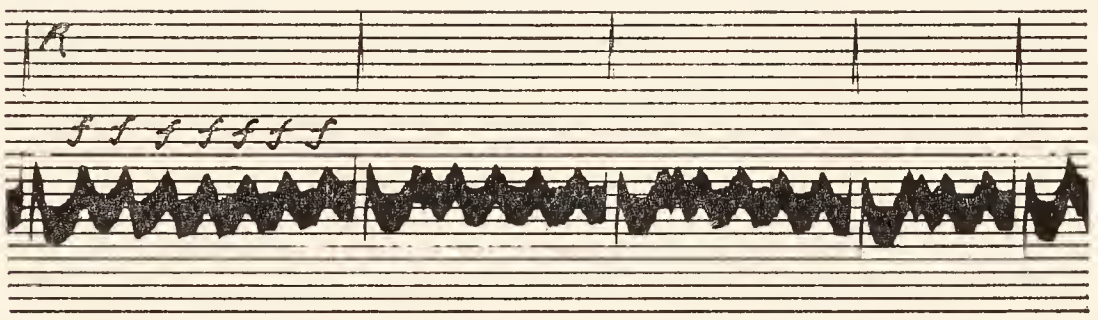


FIG. 6.—An electrocardiogram from a dog, while the auricles were fibrillating subsequent to their faradic stimulation. The curves of Figs. 5 and 6 have been chosen to illustrate their striking resemblance.

all the known phenomena of the disease in man; for auricular fibrillation could be regarded as an extremely rapid and inco-ordinate beating of the fibres of the auricle, resulting in virtual paralysis of the chamber, and in the showering of rapid irregular impulses on the ventricle. Auricular fibrillation would explain irregularity of the ventricle; it would explain the loss of all signs of natural auricular contraction, in the absence of auricular atrophy; it would explain the occurrence of tiny rapid waves in the venous records; and in the electrocardiogram it would explain the irregular complexes of supraventricular type, for all impulses to the ventricle would still come from the auricle. Given that the origin of the ventricular rhythm was a series of rapid and irregular impulses arising in the auricle, digitalis slowing, previously unexplained, at once became

interpretable as the result of heart-block ; and this interpretation was all the more acceptable because digitalis in full doses had already been shown to cause heart-block in clinical cases. Similarly, Mackenzie's specially described "nodal bradycardia," in which slow and usually irregular action of the ventricle was peculiar because associated with the ventricular form of venous pulse, could be ascribed to auricular fibrillation with heart-block of different grades due to disease of the auriculo-ventricular bundle. And this idea was confirmed almost at once from a number of sources. Thus, on looking back at the original descriptions of these patients, it was found that one case had actually displayed chronic heart-block before the slow irregular action supervened, and that others in which the pulse was very slow had suffered from the characteristic syncopal attacks usual in cases of high grade heart-block. Two of the patients were still available and re-examination of these discovered oscillations and other characteristic features in their electrocardiograms, as was anticipated ; and at a later date the auriculo-ventricular bundle of one of these was actually found to be completely broken through by disease. Thus the theory of auricular fibrillation seemed to bring a flood of light upon a number of obscure phenomena ; than which there is no surer sign to an investigator that the goal is near.

There still remained the meaning of the oscillations of the human electrocardiogram. These had either been disregarded, or had been wrongly regarded as resulting from small contractions of the body musculature. Taking a case of gross irregularity with large right auricle, special leads to the galvanometer were arranged from the chest wall, from the region of the right auricle, and from the borders of the ventricles. By this device the patient's electrocardiogram became analysed into its constituent parts, a curve of almost pure and continuous oscillations emanating from the auricular region, and a curve of almost undisturbed ventricular complexes from the ventricular region (Fig. 7). In paroxysmal cases, the lead from the chest wall best displaying the continuous oscillations was in general that which *in the same subject at another time* best displayed the ordinary auricular beat. And it may be remarked in parenthesis, that this form of control, in the same and not a different subject, is always the most valuable though not always the easiest to

be got. To resume, it was thus possible in man to trace the oscillations to the region of the auricular portion of the heart, thus bringing direct evidence of its continuous and abnormal activity; the demonstration could be repeated upon different patients, and also upon animals with actual fibrillation.

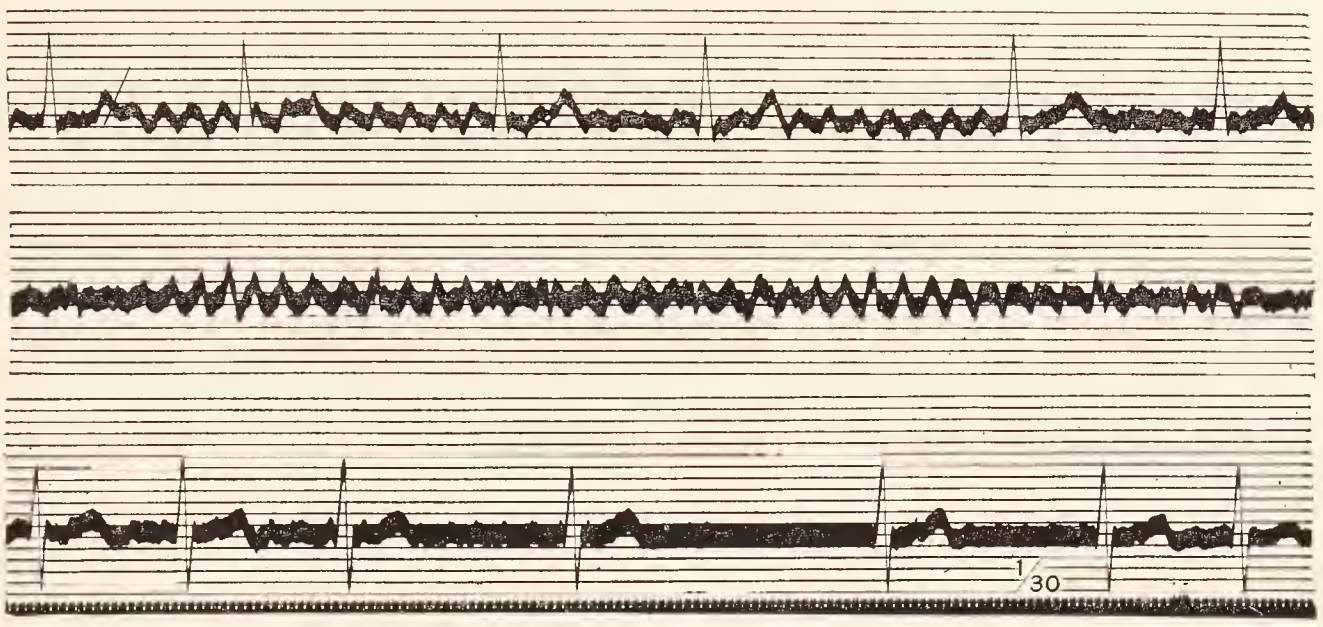


FIG. 7.—The top electrocardiogram was taken by leading from the right arm and left leg of a patient suffering from mitral stenosis and complete irregularity; in curves from such a lead both the auricular and ventricular activities are well represented. The middle curve was taken by means of two contacts placed on the front of the chest wall near the region of the right auricle; this curve consists almost entirely of auricular oscillations. The bottom curve was taken along the left border of the heart, and consists almost purely of ventricular effects.

## THE CONTRIBUTION OF ANIMAL EXPERIMENT.

It is convenient at this point to comment upon the part played by animal experimentation in the proof of auricular fibrillation in man, evaluating this method more generally by means of the illustration. It has long been recognised that in studying disease in man, the provocation of like phenomena in lower animals, and their fuller investigation in these, may be highly efficacious. It will be manifest that had the investigation of gross irregularity been limited to man himself, an understanding of the underlying disorder of the heart beat would have been hampered very seriously. The experiments showed that an apparently inco-ordinate beating of the auricle, characterised by quivering movements of the muscle, can be established in the dog, and that this gives rise to a number of abnormalities of arterial and venous pulse curves, and of electrocardiogram, very closely corresponding with phenomena witnessed in patients;

and thus gave strong grounds for the belief that gross irregularity in man has an inco-ordinate or quivering movement of the auricle as its basis. The advantage gained lay in our ability to study the auricular muscle of the animal by examining it more directly than was possible in man, and thus to gain more intimate knowledge of the nature of its disorder. But the limitation of the method must be recognised clearly too. It would be a very simple and serious fallacy to imagine that the human disease had been reproduced in the animal; it will be appreciated that it was merely an end product, namely, a particular disorder of beating, which had been provoked. No one has as yet deliberately caused the underlying process responsible for auricular fibrillation to appear in any animal. The experimenter who has provoked merely the end product must recognise the fact, and may use the method advantageously within this very strict limitation that he studies only what has been provoked. And it is obviously very important that, before applying conclusions to man, he should make sure by critical study, that what has been provoked is strictly comparable to the end product of the human disease. The caution here required is illustrated by the present example. The name auricular fibrillation was first used to designate a disorderly action of the dog's auricle arising *during* its faradic stimulation. Now, as has since transpired, this particular form of auricular disorder, or "rapid re-excitation" as it was later termed, though bearing a close superficial resemblance to what we now understand by auricular fibrillation, is by no means the same thing; and it is highly improbable that it occurs except under artificial conditions. The disorder that is now regarded as identical with the clinical one occurs only as a *long continued after-effect* of faradic stimulation, the one form of auricular disturbance provoking the other. The two are undoubtedly distinct forms of disturbed mechanism, but happily no serious error of conclusion has been discovered to have arisen from this original confusion. That was so because in actual fact, in the comparison between clinical and artificial disturbance, the after-effect was usually used as a matter of convenience, and because the argument in proof was not confined to mere comparison, but consisted largely of *direct reasoning from observations upon man himself*. The chief contribution of animal experiment was that the comparison of the disorder in patients

with that provoked in the dog pointed to the human auricle as the seat of a peculiar disturbance. It prompted a further investigation, the enquiry into the origin of the electrical oscillations ; and this led to direct evidence of such an auricular disturbance in man. Evidence of this kind, derived as it is from the patient himself, at once assumes precedence ; for it provides perfect security that it applies to the precise manifestation of disease, which it is desired to study.

### THE FINAL PROOF.

We come to a description of the last stages of this particular investigation. The experiments on animals and the clinical observations seemed to leave little doubt as to the conclusion. If we could actually view the human auricle in a case of gross irregularity, there should be visible and final proof that the auricle does not beat normally, but that its muscle presents a rapid quivering movement. The chance that such an opportunity would legitimately present itself was too remote, so enquiries were made in the hope of discovering the disorder as a natural affection among domestic animals. The search would not have been successful but for the continued interest and cordial help given by Professor Woodruff, of the Royal Veterinary College, and by the late General F. Smith, then chief of the Royal Army Veterinary Corps. Through this generously given co-operation examples of what transpired to be very rare instances of irregular cardiac action in horses were found and studied ; these presented phenomena exactly similar to the familiar ones in the human patients. The final scene was set at Bulford Camp on Salisbury Plain where in June, 1910 a gelding 16 years old and presenting the characteristic disorder of heart beat and early signs of failure with congestion, was examined. When the chest of this horse had been incised and opened, an excellently clear view of the beating heart was obtained. The ventricular beating was rapid and grossly irregular, as it was while this old horse was on its feet and conscious. At first no intrinsic movements could be seen in the auricle ; there was certainly no general shortening of its fibres ; but close inspection revealed the expected flickering movements upon the surface. Here was demonstration, and ocular demonstration, not of a condition artificially induced, but of the end product of actual disease.

Clinical science, which so largely consists of the study of what may properly be called the pathology of living man, is here shown to make use of comparative pathology of the living in solving its problem. An observation in the field of animal disease is seen to bring the idea that auricular fibrillation occurs in man at once to the position of final acceptance. It is a method of high value and one that happily is beginning to be used more widely.

A few words complete this chapter; the observations began with man; animal experimentation was called in aid; it led to further investigations in man and to direct inspection of the auricle in horses, the subjects of the natural disease. There could be but one further step to completion, namely, a view of the fibrillating auricle in man. That step has actually been taken in quite recent years by Levine and his colleagues.*

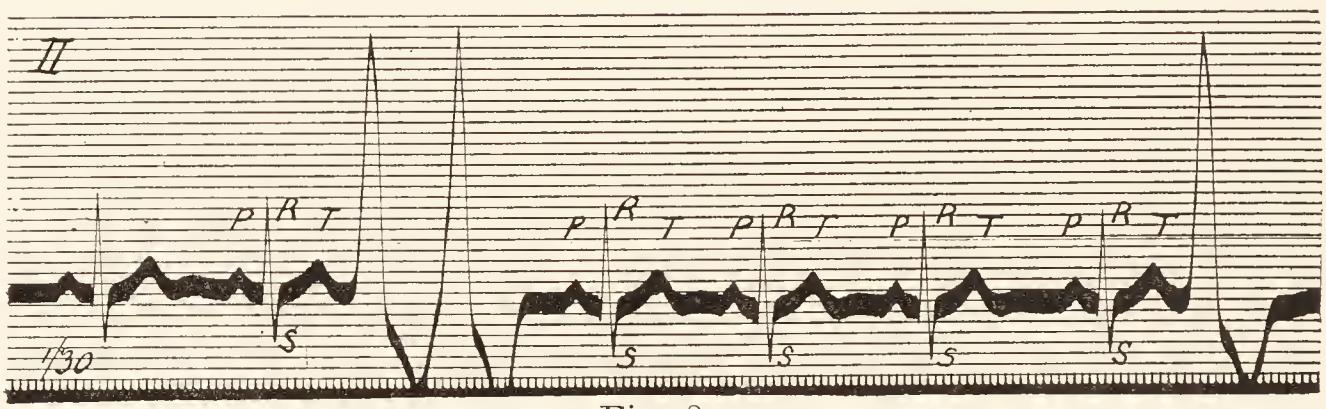


Fig. 8.

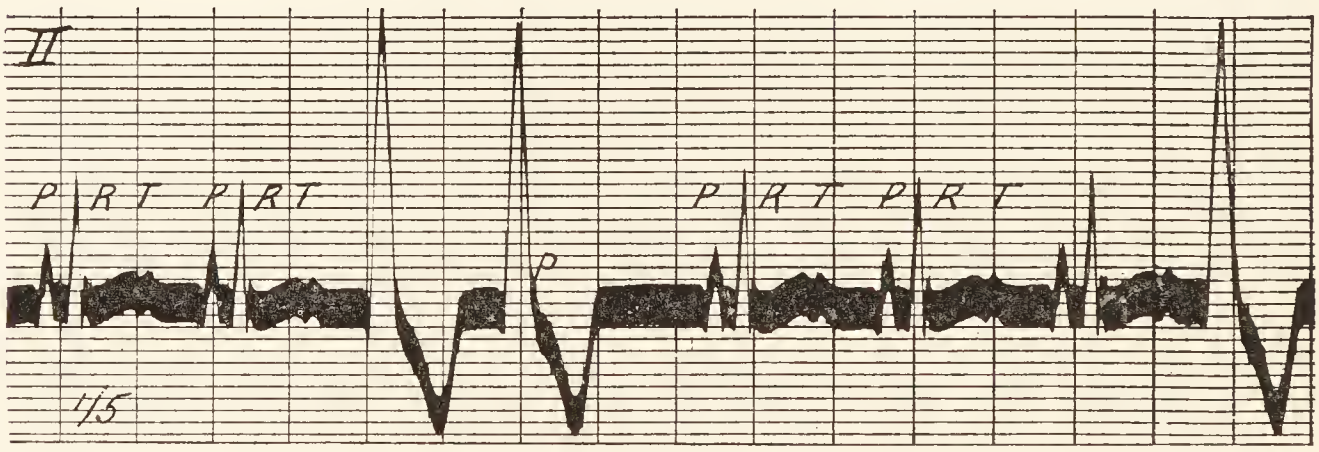


Fig. 9.

FIGS. 8 and 9.—An electrocardiogram from a patient displaying ventricular extrasystole, first a pair of abnormal beats and then a single one. Below it an electrocardiogram from a dog's heart, showing three similar abnormal beats produced by suitably stimulating the ventricle. These two figures are inserted here as a second illustration of the production in an animal of a manifestation of human disease.

*NOTE.—Full references to the original papers will be found in a historical account written in the *Brit. med. Journ.*, 1912, i, *p.* 57; and in my book "*The Mechanism and graphic Registration of the Heart Beat*," 3rd Ed. 1925. See also Cutler, Levine and Beck, *Archives of Surgery, Vol.* IX, *p.* 784.

# CHAPTER 3.

## AURICULAR FLUTTER.

### THE CLINICAL DISORDER.

The term flutter was first used by McWilliam in 1887 to describe an extremely rapid response of the auricle to faradic stimulation. The nature of the disorder observed by him cannot positively be identified to-day with flutter or with fibrillation, in the sense in which these terms are now used; but the term auricular flutter was adopted by Jolly and Ritchie in 1911 to designate a particular condition in patients in whom it soon came to be well recognised and fully studied. It displays itself by an extremely rapid action of the auricles. The rate of beating is about 300 per minute; it is so fast that the ventricle is rarely able to respond at more than half this rate, and often responds at even lower rates. The rapid action is occasionally reflected in curves taken from the veins of the neck; it is displayed invariably and well in the electrocardiogram (Fig. 10). In considering the nature of this disorder the auricle is alone of interest. The beating of the auricle is remarkable for its high rate, for its almost perfect regularity, for uniformity of rate from hour to hour and day to day, and for its usual persistence for long periods such as months or even years. Occasionally flutter occurs for shorter periods; these paroxysms begin and end abruptly. It is the rule for this rhythm to remain completely undisturbed under very varying conditions, such as exercise, emotion and vagal stimulation; in 30 records from one patient taken at intervals over a period of six months and under varying conditions, the auricular rate always lay between 260 and 278 beats per minute. In the electrocardiogram the auricular action is shown as a relatively abrupt upward, or upward and downward, movement with a more gradual return to the original base line, these movements

being repeated exactly, over and over again; the curve thus consists of a regularly undulating line upon which the beats of the ventricle are superimposed. It is notable that the movement of the recording string is incessant, the end of one cycle, if we may speak of such, passing into the beginning of the next without any intervening period of rest. Clinical observation shows that the disorder has close affinities with the more complex condition auricular fibrillation, to which it often becomes converted.

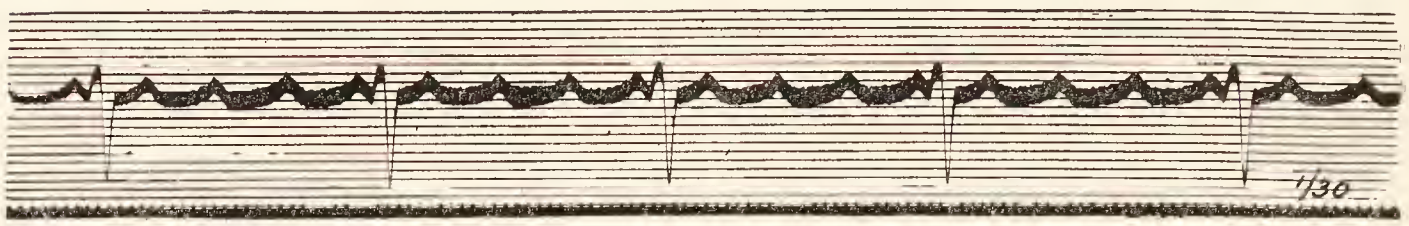


FIG. 10.—An electrocardiogram from a patient displaying auricular flutter. The auricles are beating at a rate of 276 per minute and the ventricles are responding regularly at 69 per minute.

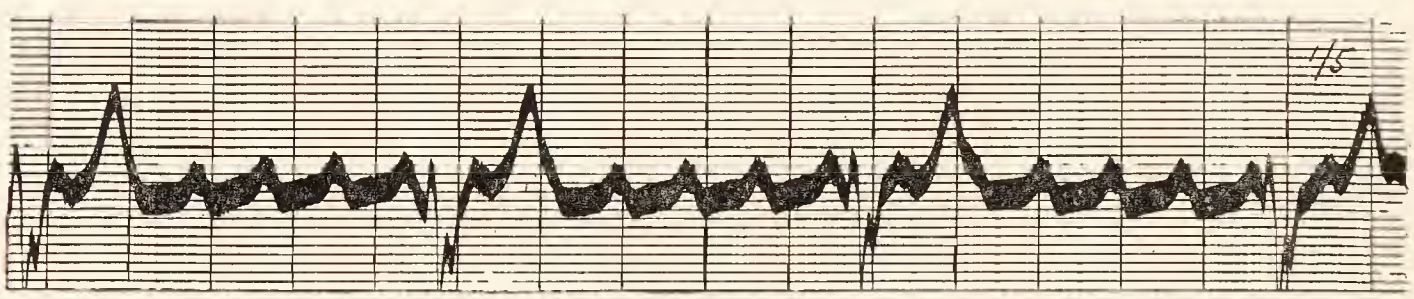


FIG. 11.—An electrocardiogram from a dog in which auricular flutter has been produced artificially by rhythmic stimulation of the auricle. The auricle and ventricular rates are 352 and 60 per minute respectively.

These facts were known to me from the writings of others and from my own studies of patients. A desire to understand the meaning of the phenomena led me to enquire into its nature.

## EVIDENCE DERIVED FROM ANIMALS.

The investigation of the nature of this rhythm began, as it could only begin, in an attempt to reproduce it accurately in animals. It was found that this could be done, though by no means invariably, by stimulating the auricle of an anæsthetised dog with induction shocks succeeding each other regularly at a rate of 350 to 500 per minute. The disorder to be established was of course one which would persist after stimulation was withdrawn, and one which in particulars other than this persistence

corresponded to the clinical disorder (Figs. 10 and 11). A very great difficulty was to establish the disorder for a sufficient length of time to permit the necessary investigations of it to be completed ; this was only rarely accomplished and the number of observations was thereby limited. It will be understood that it was not the disease as it occurs in patients that was reproduced, but merely something differing from the end product of the disease in no essential respect that could be recognised ; the natural disorder is presumably the more stable because some hidden factor predisposes to it. The purpose of establishing the disorder in the animal was that the course taken by the excitation wave in the auricle might be studied and the disorder otherwise investigated.

The method used was galvanometric and was devised, and had been used in many earlier experiments, to trace the course of the excitation wave in the naturally beating dog's auricle ; leading off electrodes were brought into direct contact with the auricular wall at suitable points, and the arrival of the wave at each of these points determined relative to a common standard. The method was of very great accuracy and simultaneously indicated the general direction taken by the wave in passing any point examined. When the heart was beating normally, the excitation was found by this method to start in the region of the sino-auricular node, which lies just above and to the right of the base of the superior vena cava near $\times$ in Fig. 12, and to spread from this region radially to different parts of the auricular surface. Such is the usual manner in which the wave distributes itself, and the fact is largely responsible for the universal present-day belief that the excitation wave arises in the sino-auricular node and spreads from this. But when the same auricle was similarly examined while fluttering, a very different state was discovered. The wave, traced as far as it could be, was found to emerge in a direction from left to right from below the inferior vena cava (as it stands in Fig. 13), to pass up the whole length of the tænia terminalis, ascending to and turning round above the superior vena cava from right to left and backwards. If we arbitrarily fix zero time as that at which the wave emerged behind the inferior cava, then it appeared successively at 0·0230, 0·0541, 0·0694, 0·0980, and 0·1130 sec. at the corresponding points marked in Fig. 12. The next wave to appear at the inferior

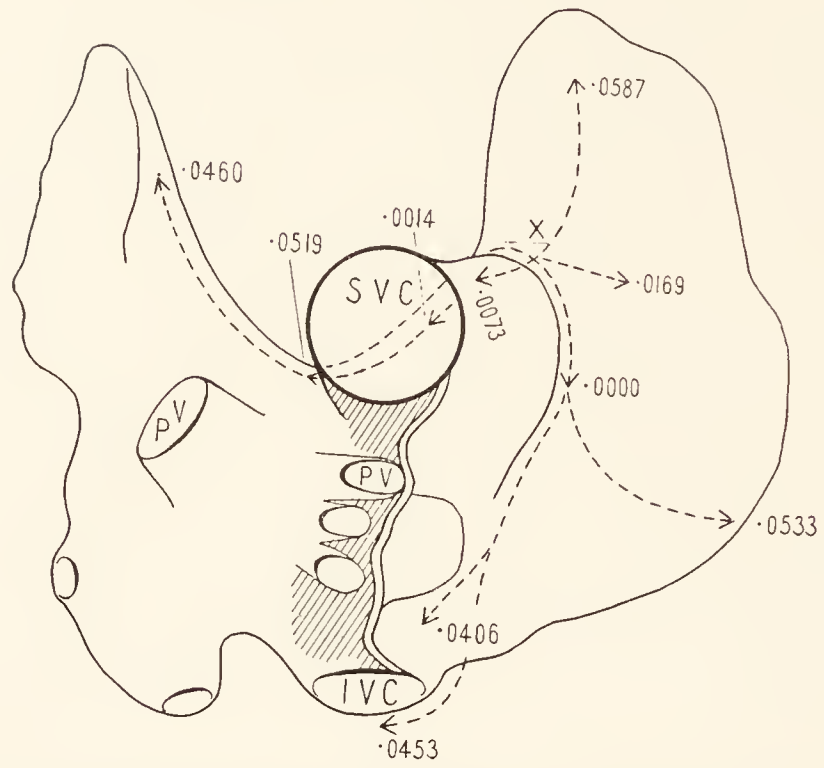


FIG. 12.—The auricular portion of a dog's heart, seen from the direction of the entering great veins. S.V.C. = superior and I.V.C. = inferior vena cava. P. V.= pulmonary veins entering left auricle. The values written on the diagram are the relative times in seconds at which the excitation wave was ascertained to reach the points marked by arrow heads. The direction of each arrow head indicates the ascertained general direction taken by the excitation wave in passing that particular point; the broken lines with these arrow heads form a plan of the spread of the excitation wave from its starting point somewhere near to X. The heart's action was normal.

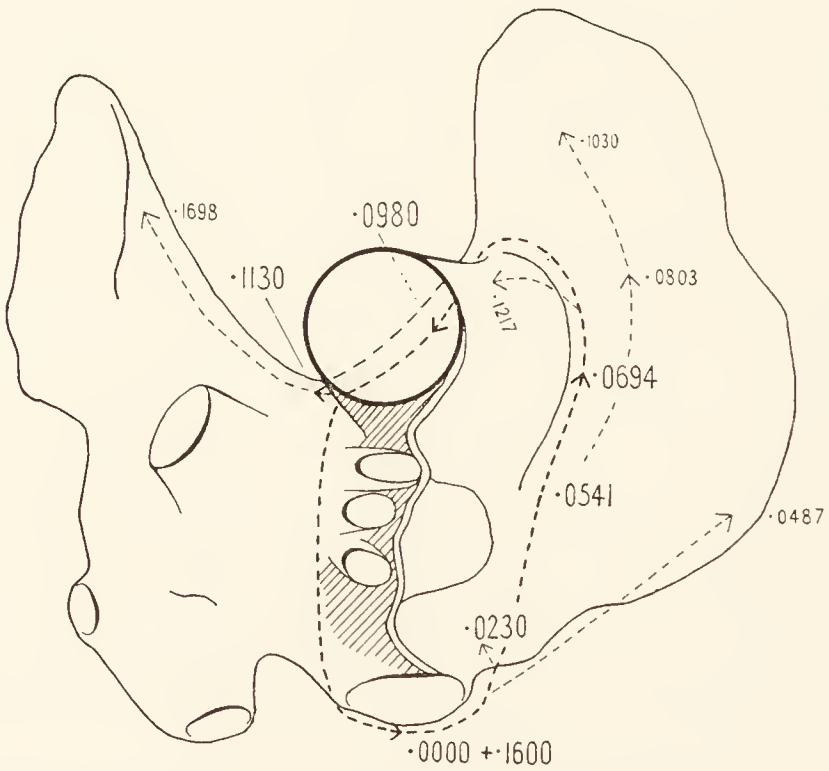


FIG. 13.—A similar chart to that of Fig. 12 showing the relative times at which the excitation wave reached the same points and the ascertained direction of its movement past these points while the auricle was fluttering in the same animal. The supposed circus is indicated by the heavy broken line, which surrounds the cavae.

vena cava, appeared at 0·1600, the natural time for its appearance with the auricular rate at 573 per minute. Was this a completely new wave, starting like the first from the heart in the region of the inferior cava, or was it a continuation of its predecessor? When the wave was at the point marked 0·1130 it was known to be travelling to the left and backwards, and when it emerged again from the point marked zero, or 0·1600, it was known to be coming from the left. The explanation might be that the wave travelled upon the course marked by arrows, and returned as a re-entrant wave at its starting point. This supposition found its confirmation in a simple calculation. The whole of the supposed circuit measured 137 mm.; it was traversed presumably in 0·1600 sec.; thus the average rate of supposed travel could be ascertained. In following the course of the wave, the longest gap was between the points marked 0·1130 and 0·1600; the distance between these points was 42 mm.; calculated on this basis the time at which the re-entrant wave would be anticipated to arrive is 0·1621 sec.; the actual time was 0·1600 sec., a very close approximation. Moreover, a similar train of waves deliberately started in the inferior vena caval region gave a pattern of spread very different from that depicted in Fig. 13; it spread, as might be expected, with equal quickness to the left and right auricles. The main experiment, supplemented by others in which the circular path of the wave was less completely traced but which showed that the path that is followed may be up or down the tænia terminalis, formed the chief evidence derived from animal experimentation upon which was based the conclusion that in auricular flutter the excitation wave performs a circus movement.

The idea of circus movement was not derived from these experiments, it came ultimately from the work of Mayer. It is of particular interest to record that his work was begun on the umbrella of the jelly fish. Romanes originally proved the tissue of the jelly fish to be excitable, and his numerous and ingenious observations led to Gaskell's well-known work on the cold-blooded heart. In 1908 Mayer cut a complete ring of tissue from the circumference of the bell and, by suitably stimulating it, found that he could induce a contraction wave to flow through the ring in one direction only. A wave so started would travel around the ring, return to its original point, pass beyond this,

and continue to circulate for hours or days. Mayer, and after him Mines, showed that the same experiment can be performed on rings of muscle cut from the cold-blooded heart. It would here illustrate no method or principle to follow the rather intricate history of how the idea of circus movement came to be applied to auricular flutter.* It will suffice to say that the experiments here described were made with the simple notion of tracing out the path followed by the excitation wave in flutter without reference to any preconceived idea; and that movement in a circuit was found to fit with this result. The knowledge that a wave may move in a circuit was derived from the dramatic experiments upon rings of contractile tissue, which were much more responsible for the application of the idea to flutter, than was the suggestion put forward both by Mines and by several workers who preceded him, that re-entrant waves may be concerned in the mechanism of ventricular fibrillation.

The conclusion that a wave moving in a circus occurs in clinical auricular flutter does not rest merely upon this experiment, here described in simplified form, though this was the starting point and remains strong evidence. The conclusion allowed

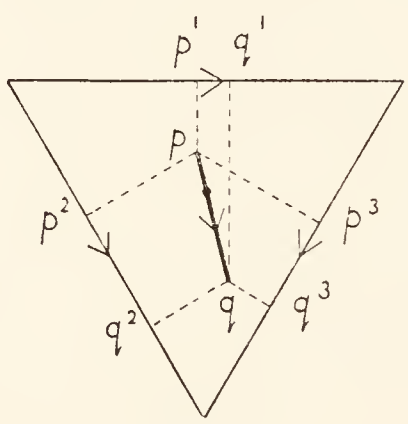


FIG. 14.

much that was previously mysterious to be explained. A wave circulating around a ring of muscle in the auricle and returning at once to repeat its course without pause, would yield a high rate of beating. Automatic return and repetition would explain the persistence of the disorder, in general a striking feature of the malady; it would explain why in the records the auricular curves are contiguous—or unseparated by isoelectric phases—for activity in the auricle is continuous. It would explain regularity of beating

* Those who desire to do so will find historical notes in *Heart*, Vol. VII, p. 229 and Vol. VIII, p. 214.

and the remarkable uniformity of rate under varying conditions and its independence of ordinary changes in nervous tone; for the rate could be altered only by change in the rate of conduction in the working muscle of the auricle, and this was found by experiment to be very stable. When by further experiments on animals, which the theory of circus movement as applied to flutter in man inspired, the muscular factors controlling circus movement became more clearly understood, this theory explained satisfactorily a number of complex responses of the auricle to strong vagal excitation, and to drugs such as digitalis and quinidine (*see* page 183); and they showed us how flutter and fibrillation could be related. Briefly, many seemingly diverse phenomena were brought together to form a relatively simple and harmonious whole, an accomplishment which without this theory was far from being possible, but one which, as previously pointed out, always brings justifiable confidence to the investigator. Convincing as the evidence seemed to us to be at this stage of our researches, yet it was built up chiefly from experiments upon dogs and therefore upon the belief, that the disorder provoked in the auricles of these animals was identical with that occurring spontaneously in man. If evidence could be obtained directly indicating that in human flutter a wave circulates in the auricle, any possible doubt arising from this source would be allayed, and the case from this and other points of view would be strengthened greatly. This evidence was now sought.

### EVIDENCE DERIVED FROM MAN.

When a wave of excitation traverses cardiac muscle, its movement is associated with the development of potential differences and of electrical currents in and around the muscle; these currents can be tapped and recorded by means of the electrocardiograph and can be used to study the direction taken by the excitation wave in the heart. When a wave of excitation is passing through a simple tract of muscle, the direction of its movement is reflected in the set of the corresponding difference of potential which develops. Thus if the movement is linear, a maximum difference of potential establishes itself in precisely the same line. When the movement is more complex, various parts of the wave advancing simultaneously in a number of directions, then the line of maximal potential difference is along an

axis, which is a compromise and reflects at any given instant the general direction of movement. This principle was established by arduous preliminary investigations into the form and meaning of the electrocardiogram in different animals, too intricate here to be described.*

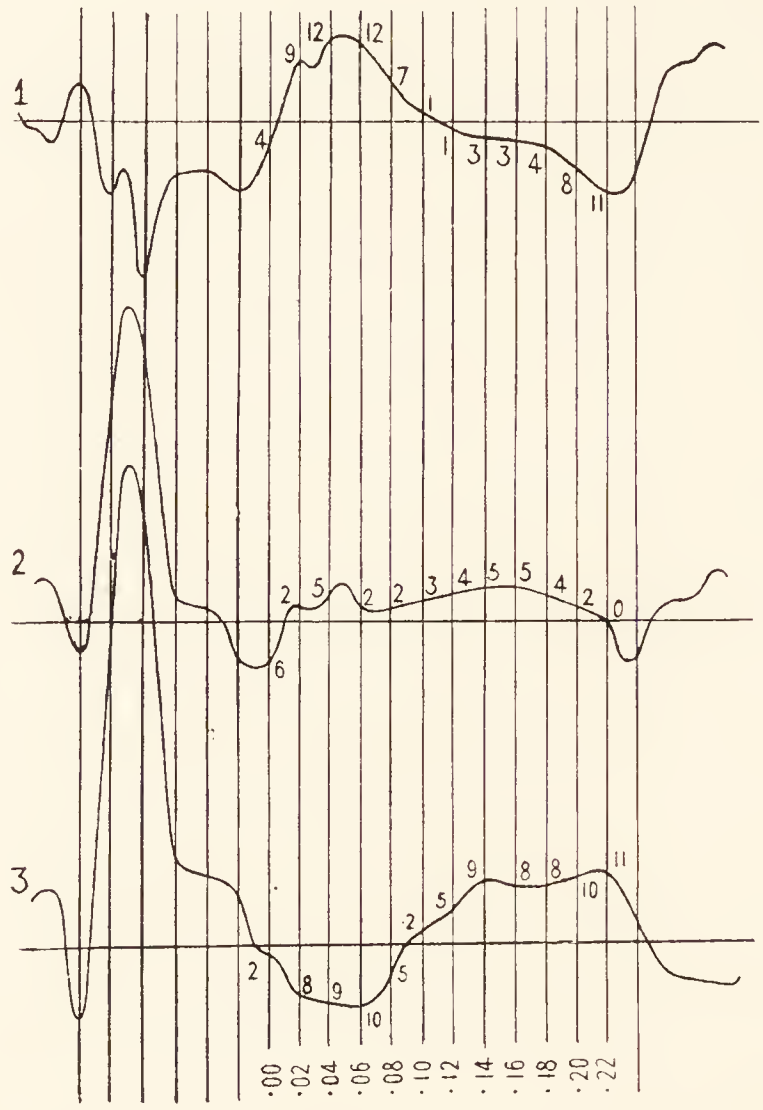


FIG. 15.—Simultaneous standardised electrocardiograms from three leads. 1, from a point to the left of the manubrium sterni to the ensiform cartilage; 2, from the same point to 7th dorsal spine, and 3, from ensiform cartilage to the 7th dorsal spine.

The curves have been retraced, vertical lines drawn through them at 1/50 sec. intervals, so that the values of the curves at corresponding times may be obtained. These values have been used in constructing Fig. 16.

To employ this principle in studying the human heart beat, the direction of the axis of electrical potential must be ascertainable at any given instant. This can be done along the lines laid down by Einthoven and his associates.† If a potential difference

* The main evidence will be found in my paper in the Philosophical Transactions of the Royal Society, 1916, CCVII, *p.* 221; a review will be found in "*The Mechanism and graphic Registration of the Heart Beat*," *London*, 1925, 3rd ed.

† Einthoven, Fahr and de Waart. *Archiv f. d. ges Physiol.*, 1913, *CL. p.* 275.

is represented in magnitude and direction (Fig. 14) by a line of length $pq$ passing through the centre of an equilateral triangle, then the relative magnitudes of the potential differences found on the sides of the triangle will be represented by the lengths of lines $p_1q_1$, $p_2q_2$ and $p_3q_3$, these being projections to the sides. It should be evident that the relative values and polarity represented by $p_1q_1$, will depend exclusively on the inclination of the line $pq$. If the value and direction of $pq$ are known, then it is a simple

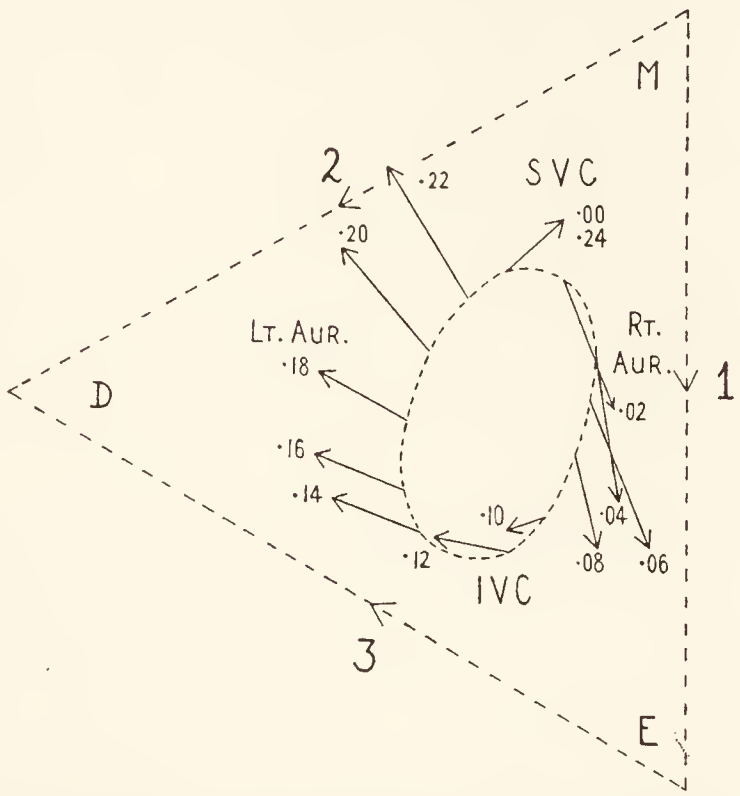


Fig. 16.—A series of arrows representing the direction in which the electrical axis of the auricle set at successive 1/50 sec. intervals, as calculated from the data of Fig. 15. The arrows show the angle made by the axis and the lines of three leads (1, 2 & 3), taken between a point near the manubrium sterni (M), the ensiform cartilage (E) and the 7th dorsal spine (D). The arrows are drawn, not to a single point, but are set in sequential order around an elipse. Their lengths represent the relative values of the corresponding potential differences.

matter, either by geometrical projection or trigonometrically, to calculate the values on the sides of the triangle. Conversely, if the values on the sides of the triangle are known, it is equally simple to calculate the value and direction of the original potential difference $pq$.

The investigation proceeded upon this basis. Upon the chest wall of a patient suffering from auricular flutter, three contacts were arranged at suitable points, making when joined an approximately equilateral triangle surrounding the auricular parts of the heart. Standardised electrocardiograms were now

recorded simultaneously from each of the three leads forming sides of this triangle; these curves are seen charted in Fig. 15. From the values of this chart, the corresponding electrical axes in the auricle could be calculated for each succeeding 1/50 sec. interval throughout the auricular cycle; the values and directions of the corresponding potential differences being represented by arrows in Fig. 16. These arrows have been arranged in relation to an elipse, a form chosen because this might be held to represent a ring of muscle around the conjoined mouths of the superior and inferior vena cava (as in Fig. 13), and lying in the particular plane of the chest in which the three pairs of leading-off electrodes (1, 2, 3) lay. The significance of the observations will be apparent almost at a glance. If a wave were to circulate around such an elipse, spreading to surrounding parts as it passed these in its circuit, the general direction of the wave and the corresponding electrical axis would change though 360° in the full cycle. This is precisely what the diagram shows the calculated electrical axis to do. The rotation of this axis as shown is not a regular one, but that is hardly to be expected, for the central muscular path in the auricle could not possibly be assumed to be a perfect ring or cylinder. Moreover, the wave in passing along its central and more or less eliptical path must be supposed to spread into various muscular appendages (as shown in Fig. 13) as it reaches them, and the activation of these appendages, irregular in size and form as they are, would naturally modify the result. But when allowance is properly made for such factors, the movement of the electrical axis is as was to be anticipated from the theory of circus movement. Thus a striking and direct evidence of circus movement in the human auricle was obtained.

## COMMENT.

Reviewing the investigation as a whole, it started as did that upon auricular fibrillation, with the separation and clear description of a disorder in the auricle of patients. The next step was the reproduction of a similar manifestation in animals, and its further investigation in these. This work, properly within the province of clinical science, was co-ordinated with contemporary and earlier work of a purely physiological kind,

which began upon the umbrella of jelly fish ; historically we are dealing with an instance of what is often, and quite rightly, emphasised, namely, that recondite researches in physiology may quickly prove illuminating to medicine. Without experiment on animals, and without this linkage with physiology, satisfactory progress could not have been made. From this stage, the investigation returned to a direct questioning of the human patient. It is important to realise that the final question was prompted by the long series of experiments on animals, some physiological, some pathological, which dealt with the tracing of an excitation wave and with simple circus movements, and that when put it was in a form rendered possible only by a further series of physical and physiological studies, allowing us to record and interpret the electrical axis and its changes of direction ; but the last observation, like the first, was upon man himself, and brought the full series of researches to a satisfactory conclusion. This instance is one which illustrates very happily the value of full linkage between clinical science on the one hand and physiology on the other. Full opportunity for medical progress is found neither in the work of wards nor in the work of laboratories ; it is found in appropriate combinations of these two.

The observations and conclusions here described led on by simple transitions and development to corresponding work upon the nature of the much commoner, and therefore much more important, condition auricular fibrillation, and to the conclusion that this disorder as it occurs in man is a form of impure flutter, also having as its basis a circus movement, but one of irregular and inconstant pattern. To describe this work would serve no useful purpose here, for it would illustrate no more than the work elucidating flutter, and the example would not lend itself to equally simple description.

Note.—The relevant papers will be found referred to in *The Mechanism and graphic Registration of the Heart Beat, London*, 1925. It should be stated that although the conclusions here given as to the nature of flutter and fibrillation are generally accepted to-day, Rothberger, *Klin. Wochenschr., Jan. 3rd*, 1922, to whose opinion I attached much weight, was unable unreservedly to accept them.

# CHAPTER 4.

## ARTERIOVENOUS ANASTOMOSES; THE OPPORTUNITIES PRESENTED BY INJURY.

### CLINICAL INVESTIGATIONS.

In 1923, I was consulted by a discharged British soldier of 34 years. He told me that he took part in an assault upon a German trench in France in 1917. He was hit almost as soon as he left his own trench, but went on. Soon he began to be giddy, black objects seemed to move before his eyes and he thought he heard bells ringing. He staggered, fell into a shell crater, and lay there, becoming increasingly drowsy. Suddenly he was moved impulsively to alertness; he sat up and saw his leg; his right thigh was bulging, pulsating and soaked in blood. He was able to draw his knife and slit his clothing to his skin; he saw blood rushing from his thigh in a pulsating jet as from a small hose pipe. He had still strength and wit enough to make a pad from a hand towel and to tie this firmly in place with the tapes of his puttees. He lay back exhausted and was rescued six hours later. When I saw him six years afterwards he complained of a lump in his right thigh and of aching pain in the leg coming soon on walking. The points at which the bullet went in and out in its horizontal course through the thigh were marked on its outer and inner surfaces. A cylindrical tumour was felt in the line of the femoral vessels and extended from the top of Scarpa's triangle down to the level of the bullet track in the lower part of the triangle. This tumour pulsated freely in systole, and displayed an intense and continuous thrill and rushing noise. The right common femoral could be distinguished as it crossed the brim of the pelvis; upon compressing this artery against the bone, pulsation ceased in the tumour. The systolic

pressure in the right was much below that in the left popliteal artery; the right leg was measurably larger than the left, its veins were unduly prominent, and the pressure readings from them were 5 cm. of water greater than on the left side. The meaning of these signs was unmistakable. The bullet had traversed artery and vein, permanently uniting their cavities; the tumour was formed by the vessels, locally swollen; the continuous thrill and murmur were due to rapid and continuous flow of blood from artery to vein; a deficient supply of arterial blood to the limb and congestion of its veins were natural consequences of this leakage. While demonstrating to students that pulsation in the tumour could be controlled by closing the common femoral artery, I noticed that with the act the pulse rate fell conspicuously and promptly. Repetition showed that the reaction could be obtained repeatedly on the right side but that the control test on the left vessel was without appreciable effect. Unaware that a similar observation on pulse rate had been made many years previously by Branham, my curiosity was deeply aroused, and the case became, with others of a similar kind, the subject of detailed enquiry by Dr. A. N. Drury and myself. In addition to the signs described, the patient presented throbbing carotid arteries, a radial pulse conspicuously water-hammer in quality, intense capillary pulsation, high brachial pulse pressure and a low diastolic reading, a systolic pressure that was greater in the left popliteal than in the brachial artery, high pulse rate, and signs of an enlarged heart; these phenomena are all common in cases of free regurgitation through the aortic valves, but of such regurgitation close search revealed no direct sign in our patient. Evidence of aortic regurgitation was not in fact expected. It will be manifest that if blood leaks from the arterial system through channels other than the natural pores provided by the capillaries, and leaks out at a sufficient rate, this will change arterial pressures; and *a priori* it would be reasonable to expect much similarity between the signs occurring when the leak is back into the left ventricle, and when it is from a main artery into its neighbouring vein. The opportunity seemed to be presented of studying not only the particular manifestations of an arteriovenous anastomosis, but the general manifestations of free leakage from the arterial tree. The occasion was the more tempting since the leak could in this

case be stopped at will by the simple act of compressing the main artery to the right leg. It was as though there were a tap that could be turned on or off from moment to moment, or at longer intervals if desired, thus allowing the state of circulation to be compared in a given subject in the two sets of circumstances. Aortic regurgitation presents no such opportunity.

While our patient was up, walking quietly or standing, his heart rate ranged at the high level of 96 to 110 beats per minute; while lying quietly it fell usually to 80 or 85 per minute. Occlusion of the right femoral artery reduced the latter rate promptly by 20 or 30 beats per minute (Fig. 17); this lower rate persisted while the occlusion was maintained; release of the vessel was

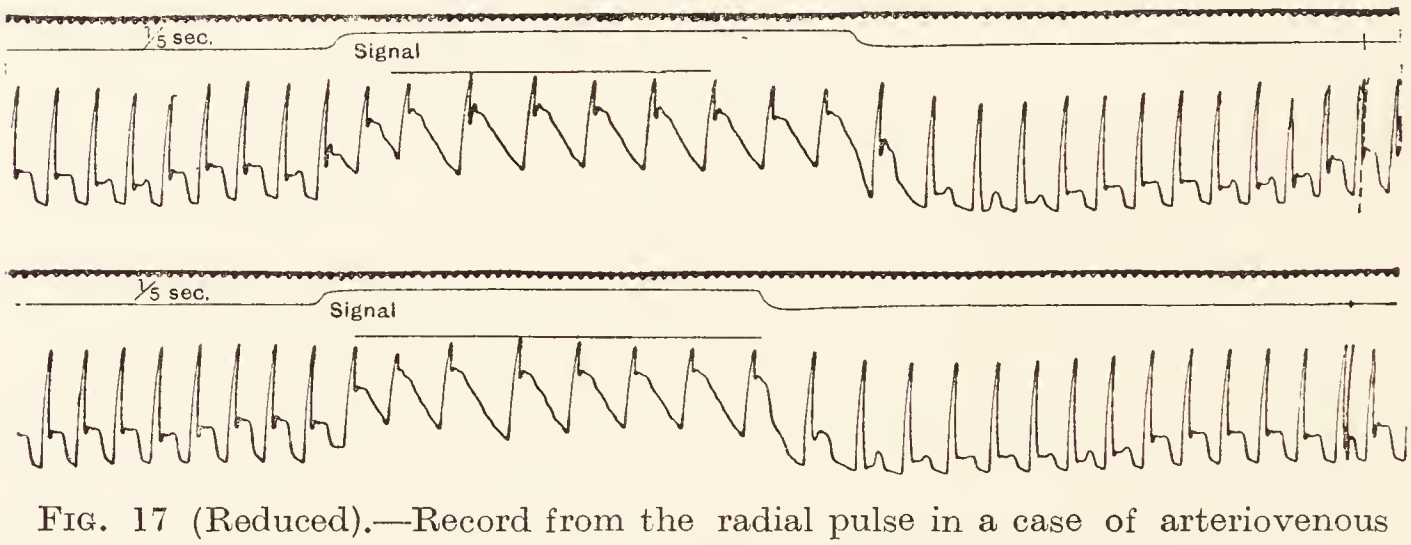


FIG. 17 (Reduced).—Record from the radial pulse in a case of arteriovenous anastomosis, showing the effect on pulse rate of compressing the artery leading to the anastomosis. The effect was to be obtained regularly, as the duplicate record indicates.

promptly followed by a return to the faster rate. Atropine, given in a dose of 1/33 grain, raised the pulse rate at rest to 130 per minute; closure of the right femoral now lowered the rate by only two beats per minute. The original fall of rate was thus shown to be produced through the vagus nerve. The readings of systolic and diastolic pressure rose in the average from 149 to 162 and from 55 to 86 mm. Hg, respectively, on closing the path to the anastomosis. The fall of pulse rate under discussion is an example, and the clearest and simplest we possess in man, of a reflex response of heart rate through the vagus nerve to a rise of blood pressure; this reflex, as Hering's work* has since shown, is started up largely from nerve endings lying in the walls of the carotid arteries.

* Hering. "*Die Karotissinusreflexe*," *etc., Dresden and Leipzig*, 1927.

The water-hammer pulse, as it is called, is characterised by its rise beginning with unusual abruptness, and is the most valuable sign we possess of reflux in patients suffering from disease of the aortic valves. In optical curves, the most exact arterial records obtainable, the pulse of free leakage at the aortic valves and of such free arteriovenous anastomosis as our patient displayed, are indistinguishable. In both the abruptness of the rise is shown by exact measurements to be of the same order ; in both it is exaggerated by raising the limb from which it is recorded ; in both the pulse is apt to display small but rapid oscillations on its upstroke, giving to the pulse a thrill-like quality. When tested in our patient these abnormal features of the pulse were at once abolished by occluding the artery leading to the anastomosis (Fig. 18). It is to be noticed that

Fig. 18. Optical record from the radial pulse before and after occluding the artery leading to the arteriovenous anastomosis. The patient was under atropine ; consequently there was no change of heart rate to influence the pulse form. Time in fifths of a second.

the change in the type of arterial curve shown in this figure was brought about while the patient was under atropine ; this was arranged of set purpose to avoid any appreciable fall of pulse rate occurring on closing the artery, for such a fall would itself influence the form of the arterial curve.

The changes found to occur on compressing the artery leading to the anastomosis would seem natural enough, and might have been anticipated. The leak from artery to vein naturally lowers diastolic pressure conspicuously, and results in abrupt filling of the arteries, and in a large pulse ; reflex rise of pulse rate follows upon lowered pressure. The demonstration that the consequences of the leak vanish when the path to the anastomosis is closed might appear to be a simple and almost redundant affair. Such would be a highly mistaken point of view ; the changes could not confidently be predicted ; the demonstration puts the

reactions beyond all doubt and brings just the security required to allow the new conclusions to be applied. If these manifestations are the direct result of the leak in arteriovenous anastomosis, then there is a strong presumption that the comparable signs are also the direct result of the leak in aortic regurgitation. The relative values of a presumptive conclusion and of a conclusion resting on demonstration may be illustrated further. The abnormal manifestations dealt with in the case of arteriovenous anastomosis did not stand alone, there was also conspicuous capillary pulsation in the lips ; there was too a curious difference in the systolic pressure of leg and arm arteries, the pressure in the left popliteal being much higher than in the brachial, a phenomenon first described by Hill and Rowlands in cases of aortic reflux. Now these two phenomena remained substantially unchanged by occlusion of the artery to the anastomosis ; therefore neither of them was the direct result of the leak ; both were consecutive to it and brought about by it indirectly. The demonstration differentiated between two series of phenomena ; *a priori* reasoning would not have done so ; it would have led to erroneous ideas regarding the second series of phenomena. Incidentally, the conclusion that these phenomena are indirect effects becomes applicable to the corresponding phenomena as these are displayed in cases of aortic regurgitation.*

From several points of view it was important to ascertain the influence of the anastomosis upon general venous pressure. Obviously pressure was raised locally in the veins into which the blood poured from the artery ; and it seemed hardly conceivable that what was regarded as free leakage from a large artery into the veins would not raise the pressure generally within them ; yet raised pressure in the general venous system was not indicated by the state of the veins of the neck or of the liver in our patient. This seeming discrepancy between theory and observation called for further work. The patient understanding and consenting, direct measurements were made by introducing a wide bore needle into the left basilic vein, and connecting this to a manometer containing a solution of sodium citrate ; the measured pressure was normal. The right femoral artery was repeatedly compressed and released while readings of the meniscus, oscillating as it did with respiration, were taken.

* The nature of capillary pulsation is considered in Chapter 6.

In this way it was established beyond any doubt that closing the artery to the anastomosis produced no fall of venous pressure and its release no rise. There were insignificant changes in the opposite directions and these happened equally when the left femoral artery was closed. The original anticipation that closure of the right artery would produce a fall, and its release a rise of venous pressure, was based upon the knowedge that general venous pressure is easily raised by injecting fluid into the veins; but this was a misconception due, as reflection showed, to the oversight that blood leaking through an arteriovenous anastomosis comes from the arteries, where it serves to maintain pressure, and thus differs from fluid introduced from without. Seemingly venous pressure failed to rise when the anastomotic tap was opened in this patient because the prompt and profound fall of mean arterial pressure reduced the flow of blood through the capillaries of the body generally. The remarkable conclusion seemed to be inevitable that the opening of a short and wide new channel can so reduce the flow through the old and narrow channels, that the amount of blood returning to the heart remains unchanged. This would mean that the output of the heart would likewise remain unaltered. It is to be emphasised that such a conclusion could not justifiably be drawn in the form of a generalisation, but only in application to cases of anastomosis in which the venous pressure is shown to be unchanged, a matter to be discussed again. The investigation naturally proceeded to a direct examination of the rate of bloodflow in the patient's sound limbs and of the effect of the anastomosis upon it, and it was anticipated that opening and closing the tap would profoundly affect the flow. This anticipation was fully realised.

Bloodflow to the limbs was studied by the well-known method of Hewlett and Zwaluwenburg. The limb being enclosed in a plethysmograph, the veins of the limb are obstructed by pneumatic pressure above the plethysmograph. The obstructing pressure (about 40 mm. Hg) though sufficient to prevent any blood leaving the limb for a time, is insufficient to obstruct the arterial inflow. The rate at which the limb increases in size, immediately after the obstruction is imposed, in these circumstances becomes a measure of the rate of bloodflow into the limb. When this method was used, repeated observations, of

which Figs. 19 and 20 are examples, gave sufficiently uniform results. The rate of inflow was increased 100% or more by closing the right femoral artery. This rise in the rate of blood-flow occurred at once on closing the right femoral vessel, as is

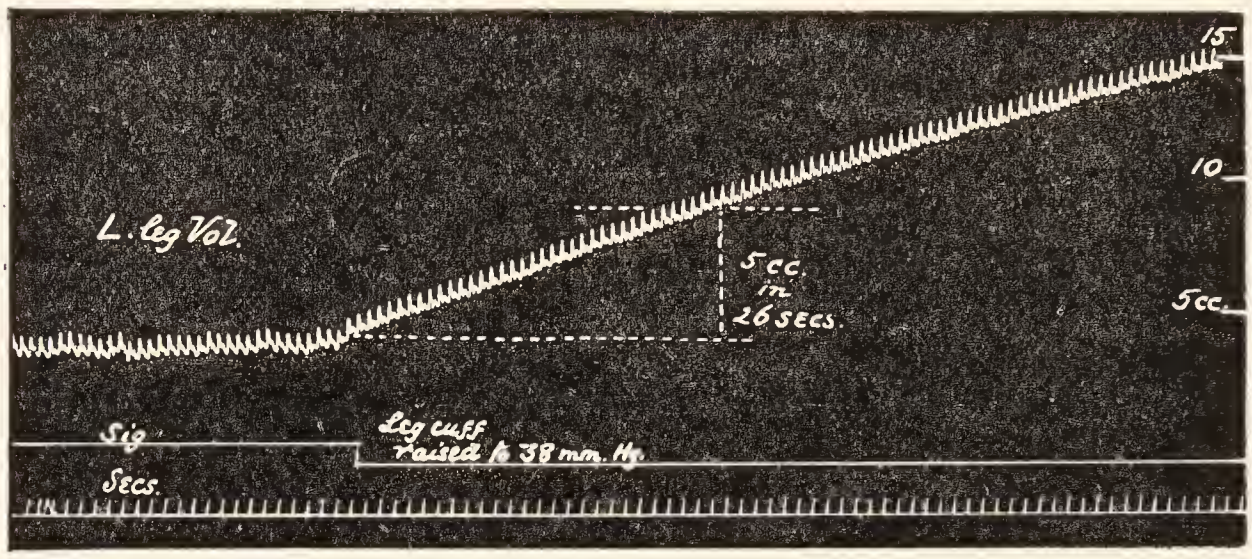


Fig. 19 (Reduced).—At first the curve of left leg volume, exhibiting pulse beats, runs horizontally. When, as marked by the signal, the veins returning from the limb are obstructed the curve of limb volume rises steadily as blood accumulates in it; 5 c.c. of blood accumulates in 26 sec..

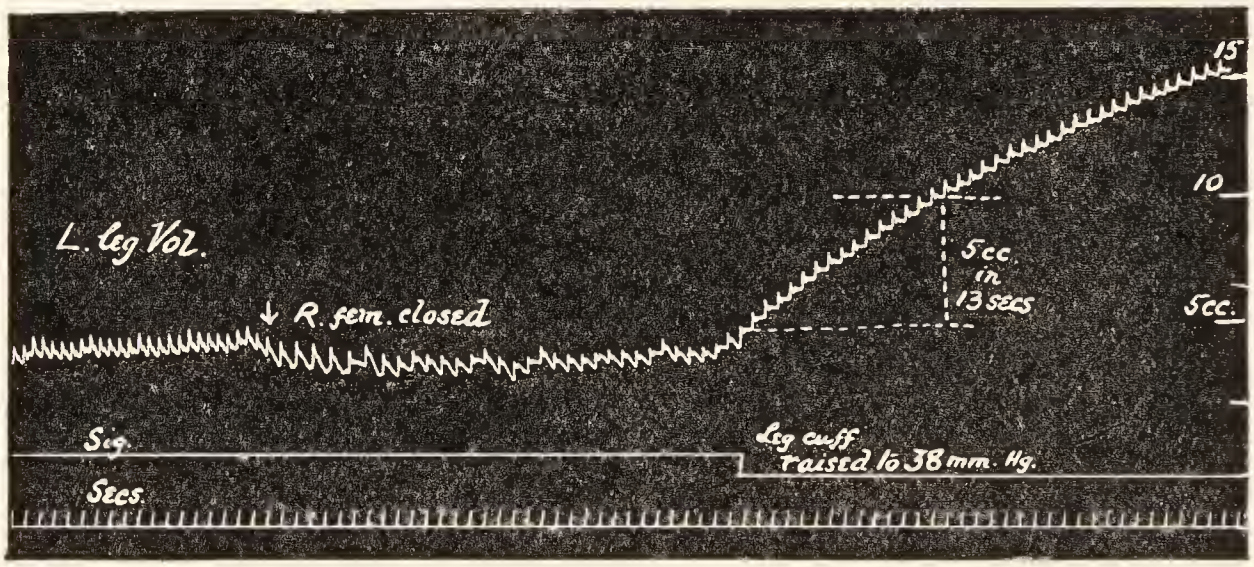


Fig. 20 (Reduced).—At the arrow, closure of the right femoral artery to the anastomosis is seen to exert little effect on the volume curve. At the signal the veins are again obstructed and the rate at which blood accumulates in the limb is now found to be 5 c.c. in 13 sec.. Closure of the left femoral artery was without measurable effect on the rate of bloodflow to the arm.

shown by Fig. 21, and as could be seen directly in the capillaries at the base of the finger nail, watched under the microscope. It rose at once and was maintained at this level; the increase in bloodflow was due, therefore, to an immediate effect exerted

directly on the arterial side. It was independent of the nervous system or of any change that could be supposed to occur in cardiac output consequent on change of inflow to the heart, for this would entail delay; the conclusion come to was in complete accord with the finding of unaltered venous pressure. Thus we were led finally to conclude that cutting out the leak caused a corresponding extra amount of blood to flow through the remaining vessels of the body. If we assumed that a doubled bloodflow through the limbs approximately represented the change in bloodflow to the tissues of the body generally, then we were forced further to conclude that in this patient, while

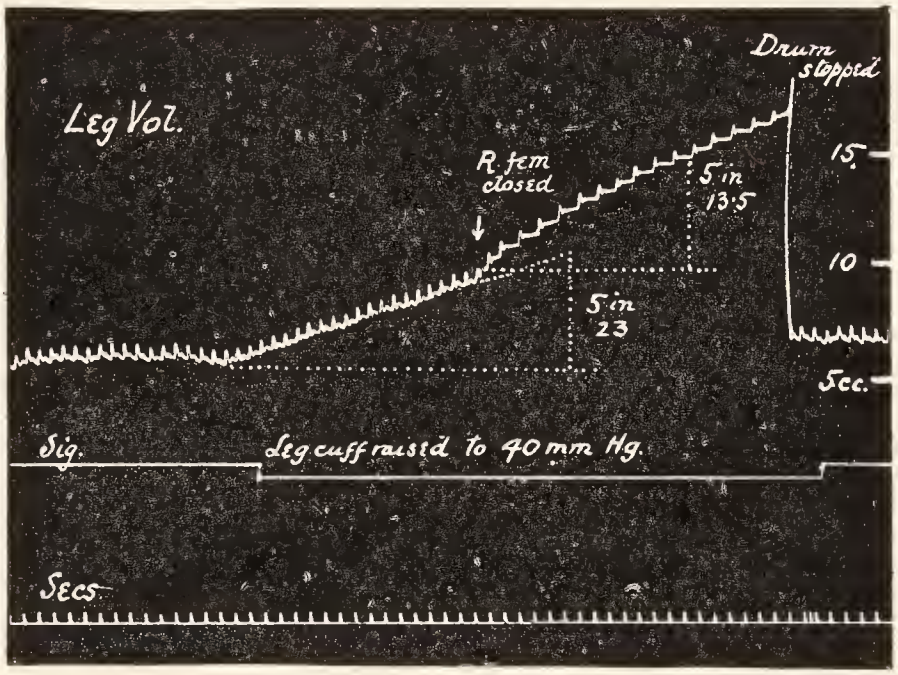


FIG. 21 (Reduced).—In this curve, the veins having been obstructed, the volume of the leg is rising when the right femoral artery is closed; there is an immediate and conspicuous increase in the rate of bloodflow into the limb.

ordinarily at rest, half the blood discharged from the heart passed through the anastomosis. Such a conclusion, unlikely as it may seem at first, is not in fact inherently improbable, since the superficial femoral artery is normally a large one, and since autopsies have shown it usually to be much dilated on the proximal side of an arteriovenous communication; it is to be remembered, too, that the blood would flow from a wide bore tube, not into tubes of small calibre and high resistance, but into capacious veins under low pressure; the maleolar venous pressure was 7 cm. water in this patient while lying horizontal. The flow from artery to vein would be very similar to that

attained were the arterial aperture in direct communication with the atmosphere. If the output of a dog's heart is measured cardiometrically and this output is compared with the output of blood from the cut external iliac artery, the latter is found to be a substantial fraction of the first; it may amount to more than half the output of the left ventricle.

It is really immaterial whether we accept or not the calculated loss of blood through the anastomosis as half the heart's output; it is only material that we accept it as a considerable fraction, which conclusion is inevitable. To what physical changes do leaks of this order directly give rise in the general arterial system? It is now clear that they produce precisely those changes well known to occur in regurgitation through the aortic valves, to water-hammer pulse, and to pulse pressure exaggerated to 100 mm. Hg. These observations therefore seem finally to terminate the controversy* as to the amount of blood regurgitating in clinical cases of aortic disease. Given that the arterial phenomena are as fully developed as in this case of arteriovenous anastomosis, and this is not unusual, then the blood regurgitating is a considerable fraction of what is ejected at each beat.

The investigations described are put forward in illustration of a purely clinical research. This yielded in the first place new information about the effects of arteriovenous anastomosis upon the circulation, some of it not without interest to physiology; but that was not the end point, for in the second place this information became relevant and important to an understanding of the manifestations of a distinct and much commoner disease, namely, of the aortic valves. There is another and more general direction in which knowledge of arteriovenous anastomosis and its effects on the circulation is seen to be important. The closure of the vessel to such an anastomosis raises mean arterial pressure substantially and consequently increases conspicuously the flow of blood from arteries to veins through the capillary bed. There is no other known condition or way in which either of these changes can be brought about in man so quickly, so effectively, and in so simple a manner. If pressure is raised by the use of drugs or by exercise, the changes in the subject are

* The very serious difficulties standing in the way of any direct measurement of the blood regurgitating through valves artificially ruptured in animals are discussed in the original article, in which references will be found (*Heart, Vol.* X, *p.* 350).

of greater complexity and interpretation is correspondingly difficult. A case of arteriovenous anastomosis of the superficial femoral vessel is one to which question after question can suitably be put, with the prospect of obtaining truer answers than can be obtained from any other source. It has been seen how our patient served to display the striking effects of blood pressure change on pulse rate in man; the same case was used to study the effects of changed blood pressure upon pulse wave velocity, and upon the intensity of the second aortic sound. It was used to determine the time relations and extent of a rise of skin temperature, brought about in response to increased bloodflow started and stopped at will (Fig. 22).* It is a type of case to

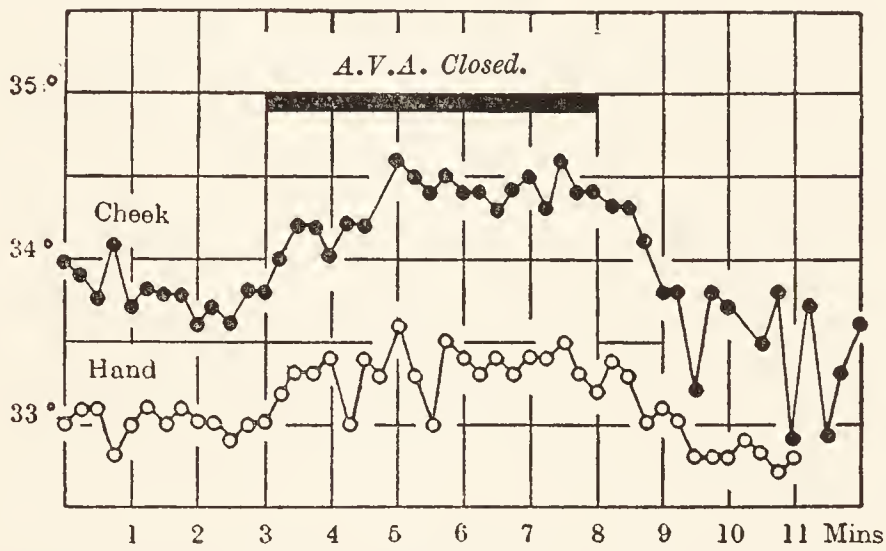


FIG. 22.—Curves of temperature of the cheek and hand; showing the effect of raising the rate of bloodflow through the skin by closing an arteriovenous anastomosis. Although the change in bloodflow takes place abruptly, the rise of temperature is not completed for two minutes.

which very many enquiries may still be addressed profitably in future times. It has the special virtue of providing its own and most appropriate control; the comparison of a given phenomenon is not instituted between abnormal subject and normal subject, but in one and the same subject while in an abnormal and normal state.

## INVESTIGATIONS IN ANIMALS.

Having observed a number of circulatory changes, consequent upon arteriovenous anastomosis in man, and having drawn from them certain conclusions, we considered it desirable to

* *Heart, Vol.* XI, *p.* 188.

seek confirmations and extensions of these by experiments on animals. I have deliberately refrained from incorporating these results in the previous account, so that the value of the clinical observations and conclusions may be assessed more readily, and also so that the order of description may in fact follow the order of observation and conclusion. It is important in this connection properly to adjust the perspective between the clinical and the laboratory study. In leaving the patient and turning to the animal we must recognise in its full significance that we no longer study the effects of arteriovenous anastomosis in man, but in a differently made creature. The special value of the animal experiment is that by utilising it we enjoy greater freedom of action, can explore where we cannot explore in man, and can employ more direct methods of registration, thus gaining new or more accurate information. On the other hand, we employ animals under full anæsthesia, which in itself modifies circulatory conditions and is very apt to interfere with the normality of vagal tone and with natural vagal reflexes; against fallacy arising from such sources it is necessary to be on guard. Lastly, if the experiments are to be undertaken upon animals which do not regain consciousness, only the immediate effects of opening and closing the anastomosis can be studied, to the exclusion of remote sequential changes, which are actually known to appear in the clinical case. The safeguard is to cling to the facts established for man himself; where observations on man and animal are in harmony, the new observations will give support; if they are in discord, the observation on the animal must not automatically be allowed precedence; precedence must be given to one or other on a reasoned basis when the discord is understood. Actually in the present instance we shall not be called upon to discuss conflicts of evidence; these remarks are for more general consideration. Conflict was avoided, as it usually can be avoided, by mode of procedure.

The object of the new enquiries, in so far as they are here to be described, was not the mere study of arteriovenous anastomosis in the animal, although this, had it been undertaken as the initial study, might have possessed intrinsic interest; it was to throw light on specific examples of anastomosis in man. Thus in establishing a leak between artery and vein it was necessary to be able to judge that this leak was or was not

comparable in its degree to that already studied in man; the guide was in the behaviour of arterial and venous pressures.

Anastomosis was established by using Crile's cannula, which permits end to end union of artery and vein while maintaining a complete lining of endothelium. Usually, union of the superficial femoral artery and vein in dogs establishes an insufficient leak, and union of external iliac artery and vein too free a leak. It was found, however, that the latter may be controlled subsequently by narrowing the junction a little, and that anastomosis of this order can be made to produce in

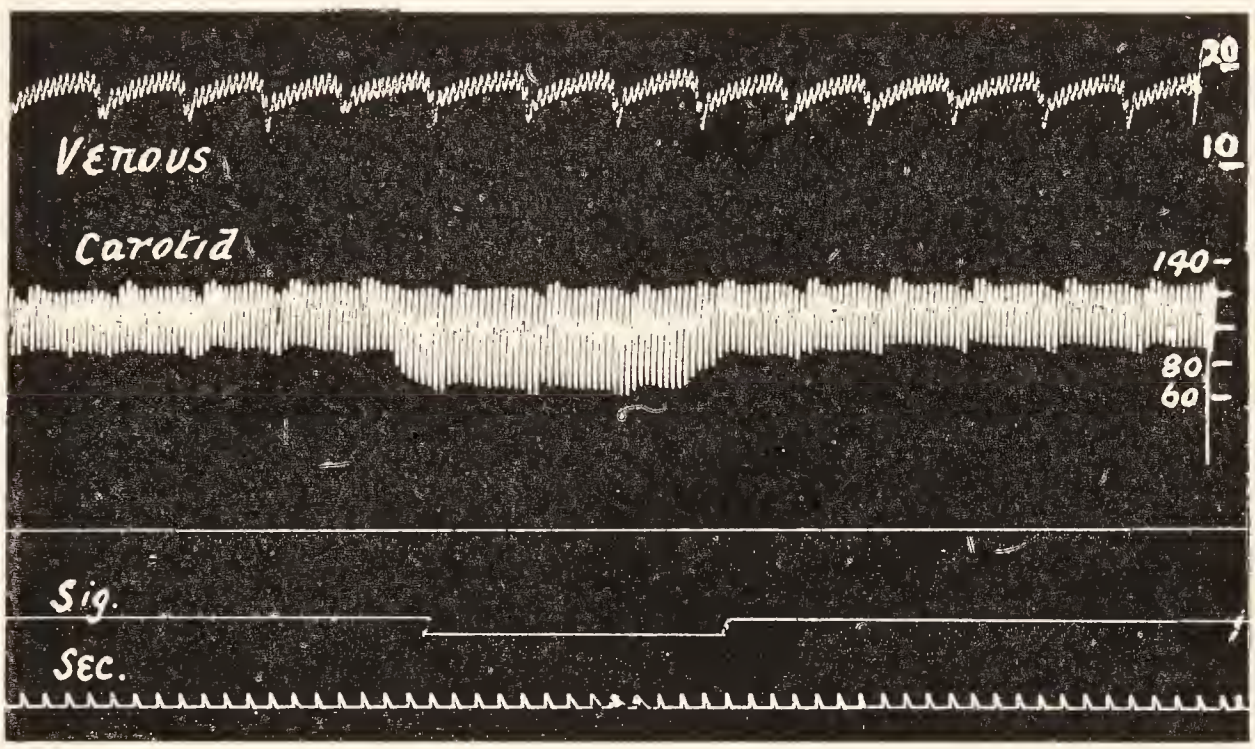


Fig. 23.—From a dog in which the external iliac artery and vein had been anastomosed together. The top curve is of venous pressure and shows small pulse beats and conspicuous fluctuation with the natural respirations. The carotid curve was taken with a Hürthle membrane-manometer. When the arteriovenous communication is opened (see signal), carotid pressure, and especially diastolic pressure, falls; but the venous record remains unchanged. The venous curve is calibrated in mm. water and the arterial curve in mm. Hg.

dogs just the effects required; thus the first step in our tests was soon accomplished. Using direct manometric inscription to surplant the indirect methods employed in man, the anastomoses were found to lower systolic pressure a little, to lower diastolic pressure a lot, while the pulse pressure was much increased. More important as a confirmation was the fact that a leak sufficient to produce these changes in arterial pressure could leave venous pressure unchanged (Fig. 23). Criticism

that the vein used for pressure measurements in man lay too far from the heart was swept away by connecting the venous manometer in the dog with the interior of the innominate vein or superior cava. In the same series of experiments direct volumetric measurements of the heart's output showed that this output remains unchanged if venous pressure stays unaltered, confirming the deduction drawn in man. If the leak from artery to vein is sufficient, venous pressure will rise, and in this circumstance and in this only, does cardiac output increase (Fig. 24). It is to be stressed that experiments in which the

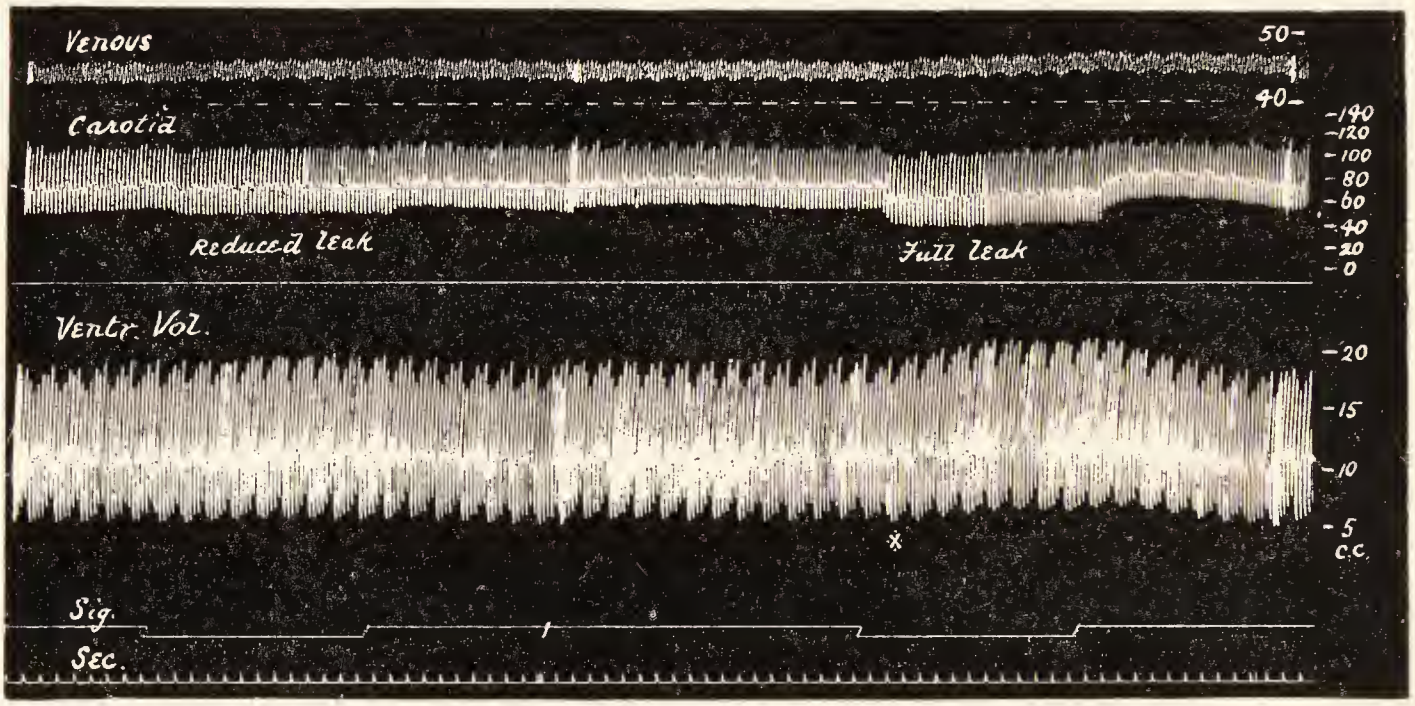


FIG. 24 (much reduced).—From a dog in which the external iliac artery and vein had been anastomosed together. Venous and arterial pressure curves, taken simultaneously with a ventricular volume curve. The figure shows the effect of opening the anastomosis partially (to the left) and completely (to the right); illustrating the increased effect on arterial and venous pressure of increasing the leak, and the close relation between the rise of venous pressure and the rise of cardiac output.

opening of an anastomosis raises venous pressure, while very relevant to the general consideration of the circulatory changes in arteriovenous anastomoses, were irrelevant to the precise point of our enquiry, which concerned the changes in a more usual type of patient with which we were actually dealing and which presents no rise of venous pressure.

In the same series of experiments optical records of the pulse taken from within the artery confirmed the appearance of a quick-rising pulse as recorded through the arterial wall in man.

A "Stromuhr" fixed upon the carotid artery gave direct measurements of the increased flow of blood in this vessel on closing an appropriate arteriovenous anastomosis; the percentage increase (up to 52%) though less than that estimated in our patient was of the same general order of magnitude.

The experiments on animals cited formed a series wholly inspired by work on patients; they added no new idea of importance, but helped to give precision and finality to some of the previous conclusions. They help to show how far purely clinical observation and experiment can take us unaided.

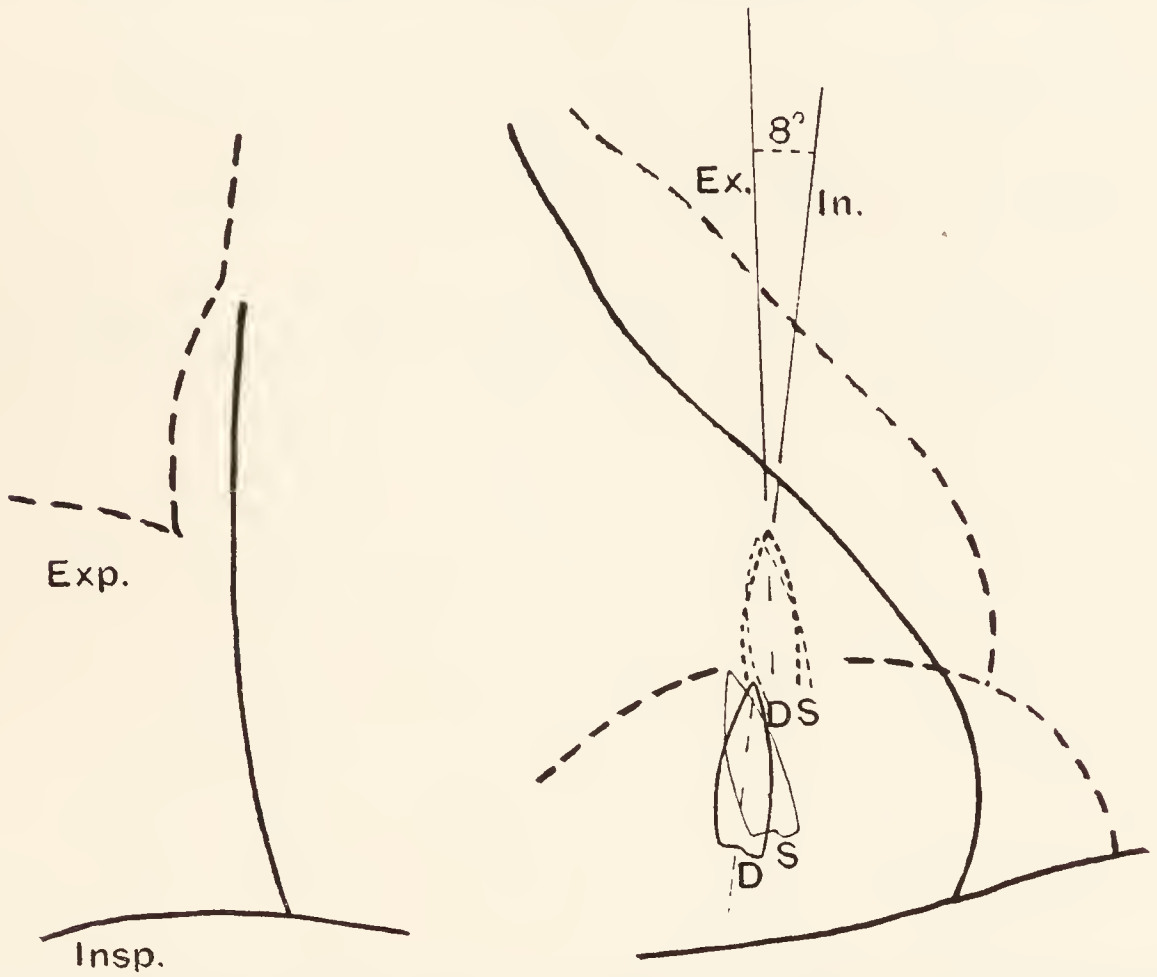


FIG. 25.—A case of bullet wound of the heart. Outlines of the heart and bullet in full inspiration (unbroken outlines) and full expiration (broken outlines), traced from X-ray plates. The systolic (S) and diastolic (D) positions of the bullet are shown. The axis of the bullet in diastole moves anticlockwise through 8° in expiration.

## OPPORTUNITIES PRESENTED BY INJURIES.

These investigations upon arteriovenous anastomosis have been introduced primarily to illustrate one of the ways in which injuries of the human body present opportunity for investigation, a matter already commented upon in the opening chapter.

A curious injury from which information of a special kind was obtained is illustrated by Fig. 25. This represents accurate

outlines of the heart of a soldier surviving from a wound received in the Great War. A bullet firmly and vertically embedded in the muscle of the heart allowed the movement of the heart's anatomical axis with respiration to be estimated with unusual precision, and to be compared with the movement of the electrical axis determined electrocardiographically in the same circumstances.

Patients in whom cutaneous nerves have been transected by accidental cuts, those in whom the cervical sympathetic or Gasserian ganglia have been excised surgically, form other illustrations; they provide invaluable testing grounds of the effects of nerve supply on many reactions (*see* page 101). There is probably no type of injury out of which ingenuity or special opportunity cannot wring new information; injury provides an inexhaustible source of knowledge.

NOTE.—The original papers and references will be found in *Heart, Vol.* X, *p.* 257, *p.* 301 *and p.* 365; see also Harrison, Dock and Holman, *Heart, Vol.* XI, *p.* 337, for further observations and references.

# CHAPTER 5.

## ACTIVE CONTRACTION OF CAPILLARIES.

In the winter of 1915-1916, while examining and treating a number of young soldiers, invalided from service for ill-health, my interest became awakened in certain reactions of the skin, which many of the young men displayed, and with Dr. T. F. Cotton and Dr. J. Slade I began to investigate them. Among these reactions was a phenomenon that had long been recognised by other clinicians, namely, the white "tache," or "ligne blanche" of the French. This white line, so it has since transpired, is not a phenomenon peculiar to any particular disease; it can be provoked with ease by stroking the skin in most normal young people, being especially well displayed upon the skin of the back, but also on other parts like the forearm, and especially if the skin is previously a little flushed. One stroke with the pad of a finger usually suffices, using a pressure similar to that required to seal an envelope; though a better way is to stroke the skin with the square end of a flat ruler. Done in either way, it will be observed that as the stroke proceeds it leaves behind a short wake of pallid skin, which, however, is lost almost at once as blood flows back into the depleted vessels and the original colour of the skin is restored. But in the space of about fifteen seconds all the skin that has been pressed upon begins to pale again, and it now pales progressively until, in favourable instances, it may stand out in a half to one minute as a vivid white band upon the skin. This mark persists for several minutes, gradually fading away. In gazing at this vivid white band our attention became riveted upon the extraordinary crispness of its margins. All over the area that had been touched by the ruler the pallor was full and uniform, ending abruptly in the straight lines of its lateral borders. Now the white band

was not due to a simple expression of blood out of the skin, but was a subsequent event as has been described; it was due, therefore, to some active reaction of the tissues that had been pressed upon, occurring after an interval of delay. Lapinsky indeed had ingeniously suggested that it might result from contraction of the involuntary muscles of the skin, such as the muscles erecting the hairs; but this explanation was clearly inadequate, for it was easy to show that the white line was unaccompanied, except perhaps at first, by goose skin, and that erection of the hairs produced no comparable pallor. Manifestly the white line must be due to contraction of the walls of blood vessels in the skin. But this idea soon brought us to a position of uncomfortable heterodoxy. It is to be remembered that contemporary physiology (1915) taught that while the arterioles are capable of strong contraction, the minute vessels or capillaries are merely passive tubes. At first, therefore, we seemed forced to regard this white band as the result of closure of the arterioles of the skin, the minute vessels, which give colour to the skin, passively decreasing in size merely because of the fall of pressure within them. But as warning against this conclusion stood the straightness of the two edges of the white band. It seemed inconceivable that the closure of vessels other than those of microscopic size could bring such a result. A test was desired, which would enable us to decide this question whether the vessels giving colour to the skin, capillaries in the physiological sense, were emptied by their own active contraction, or by passive drainage following arterial closure. This test was found when the idea came to repeat the stroke after arresting the circulation to the skin.

It will be obvious that closure of arterioles cannot empty minute vessels through which no blood is flowing; if, therefore, a white line could be obtained after arresting the circulation to the corresponding area of skin, it would have to be attributed, not to closure of arterioles and a passive emptying of the minute vessels, but to active contraction of the minute vessels themselves. Choosing subjects in whom the white line was easily provoked in the skin of the forearm, a pneumatic cuff was fixed upon the upper arm, and the pressure in it abruptly increased above systolic pressure, thus bringing the circulation to an end in the limb. This experiment showed that the white band

appears and fades in much the same time whether the circulation is previously arrested or not. Thus a reply was obtained by a simple but crucial test. In using this test two minor precautions must be taken. Firstly, enough blood must be left in the skin to give it ample colour but not to congest it deeply, so that while the white band may show up by contrast, the work of the small vessels in expelling their contents is not unduly increased. This is effected by holding the arm at an appropriate level while its circulation is arrested, and this act should leave the colour of the skin much as it is in the other arm as this hangs down. Secondly, an interval of time must be allowed to elapse, so that forward movement in the vessels below the obstruction has ceased, and the pressure equilibrium has become established in the vessels, before the skin is stroked ; otherwise it might still be conceivable that arteriolar contraction would decrease the blood content of the minute vessels. An interval of one minute is sufficient for this purpose.

Apart from the crucial test, there was this further and almost equally cogent argument. When the white band had developed on the tinted skin of the arm in which no blood was flowing, pressure upon the tinted skin with the pad of a finger blanched that skin, but as soon as the pressing finger was raised, the blood quickly returned and obliterated the mark ; yet all the time the white band remained unaltered. The blood that gives colour to the skin lies in surface plexuses of minute vessels closely intermeshed and communicating ; press upon the skin and the blood under the finger is forced out into the surrounding meshwork ; raise the finger, and it flows back to its original place. This was simple enough to understand ; but what was not simple to understand in the light of contemporary theory, was the failure of the blood to re-enter the corresponding vessels of the white band. That could be explained only if these vessels excluded blood by the tight contraction of their walls.

An approximate measure of the force exerted by these vessels on their content might be obtained by previously raising the pressure in them artificially. For this purpose the pneumatic cuff was again employed to impose a known pressure on the veins returning from the arm, thus raising the pressure in their minute tributaries in the forearm. The degree of venous engorgement requisite to prevent the appearance of the white

band as a reaction to stroking was tested, and it was found that the capillaries are capable of exerting an active constrictive force of at least 30 mm. Hg ; a value which was later raised. Heterodox or not this conclusion of contractile capillaries could no longer be placed on one side. The stroke probably produces contraction of the minute vessels by placing these under tension. Similar blanching of the skin occurs shortly after briefly stretching the skin between two fingers laid upon the skin an inch or two apart. Other forms of stimulation were investigated. Using adrenalin to blanch the skin instead of the stimulus of the stroke, it was similarly possible to show that this substance acts directly on the minute vessels and that its constricting action is not confined as had hitherto been thought to the arteries and arterioles.

When past records were now searched, statements were found in the early writings of Stricker, that he had seen vessels in the tails of tadpoles, and in the nictitating membrane of the frog's eye, diminish in calibre in circumstances that he regarded as precluding any other explanation but active contraction. These observations by Stricker had been discussed many times by physiologists, but being highly difficult to demonstrate, had obtained little or no credence. The observations upon human skin, so easy to repeat, and to us so convincing, gave us courage to put forward again Stricker's conclusion, redirecting attention to his early work, and to its confirmation by Steinach and Kahn, and stating that the burden of proof seemed now definitely to lie with those holding a contrary view. Dale and Richards were engaged at this time in unravelling the action of histamine upon the blood vessels, and were being brought by their independent observations to the conclusion that the effects witnessed by them could not be explained unless the walls of both capillaries and arterioles possess tone, which varies independently in the two structures ; they were strengthened in this belief by our interpretation of the white band. The publication of these papers re-awakened interest in the physiology of the capillaries, and led to the further repetition and to the acceptance of the early experiments of Stricker ; it played the chief part in developing our modern conception of regulation of the circulation by the minute vessels of the capillary order.

The investigations on human skin here described are first notable for their simplicity. Memory is still fresh of a feeling I then experienced, coming from the complex work of electrocardiography, that facts won with so little technical effort must somehow be inadequate, and of a diffidence in spending time in pondering upon and subsequently displaying and reasoning from phenomena seemingly so trivial. But such a deeply mistaken view could not continue, a little contemplation taught that in fact much virtue lies in the very simplicity. The investigations described fixed irrevocably in my mind the importance of striving fully to realise clean-cut facts, for however trivial a fact may seem at first sight, there is none that is infertile ; knowledge of other facts, a conclusion, or some day perhaps a generalisation will come of it. Simplicity enables the phenomena observed to be repeated readily. For this reason and because they can be demonstrated with ease to the unaided vision, the phenomena described become convincing. Most important is it that in simple experiments, such as are described, there is minimal disturbance of the living structures concerned in what is evidently a delicate reaction. The reaction studied is in fact a perfectly natural one, for the skin is often submitted to the appropriate friction and stretching during ordinary acts of everyday life ; though how the reaction is purposeful has not been determined.

These investigations are of special interest to medicine because, like so many others that will be described in this book, they came out of an examination of patients ; they were done upon the human skin and the conclusion reached applies directly to the minute vessels of man, a fact which at once adds to its importance. For in clinical science man should be the alpha, as he is always the omega, of study. The present instance too is one of many that might be cited of a simple clinical observation contributing conspicuously to current physiological theory.

Lastly, in connection with these observations, it is interesting to ponder on the reason why so simple a demonstration should have failed to be made previously. The reason is not, I think, obscure. Although the white band, as has been stated, is readily and often vividly elicited in normal people, this was not realised. It is a characteristic of the human mind to regard almost every natural phenomenon, with which there is little familiarity, if

not as supernatural then as at least abnormal. Though it does not seem to have been numbered among "devil's marks," this white band, like the respiratory arrhythmia of childhood, was judged to be a "sign" (or shall we say a portent) of this or that departure from good health. The point is neither uninteresting nor uninstructive. Faced by patients, perhaps by actual suffering, the clinician's mind is often pre-occupied with desire to identify disease and to deal with it remedially. But concentration upon the practical, or diagnostic, significance of a phenomenon, while it leads thought into what may often prove to be a sterile channel, tends to divert attention from the meaning of the thing, an enquiry that in the course of time is always fruitful.

NOTE.—A fuller account of the experiments here described, and the relevant references, will be found in the original articles, Cotton, Slade and Lewis, *Heart*, *Vol.* VI, *p.* 227 ; Lewis, *Heart*, *Vol.* XI, *p.* 109 ; Dale & Richards, *J. of Physiol.*, *Vol.* LII, *p.* 110. The subject in its further development is fully described in my book "*The Blood Vessels of the Human Skin and their Responses*," *London*, 1927.

# CHAPTER 6.

## CAPILLARY PULSATION.

The present chapter on capillary pulsation is introduced into this book primarily because it illustrates a method of approaching clinical problems more clearly than would otherwise be possible from personal experiences. I am conscious in deciding to incorporate it that the phenomenon discussed may seem trivial. But it may be pleaded—and this finally persuades me to include the chapter—that a proper evaluation of any phenomenon commonly displayed by man has importance in helping to bring precision to thought and work in clinical science. It has often seemed to me that a chief obstacle to clinical progress is that so very many of the statements of fact and of interpretation, with which we are familiar, rest on a foundation that is as yet insufficiently secured, so that accepting them as safe we are in grave danger of pitfall, or hesitating to place our weight upon them we fail to advance ; and this point of view is worth consideration in respect of things great and small, for of both is the ground under our feet composed. Although capillary pulsation may seem a slight affair, a proper understanding of it has in fact frequently proved of value in helping us to interpret the state of the circulation in other investigations.

Before proceeding to the main argument, which relates to the mechanism of capillary pulsation, it will be convenient briefly to describe the phenomenon, as seen with the naked eye and under the microscope. When " capillary pulsation " is present in the skin, whether this occurs without outside interference, or whether it is brought to view by exerting gentle pressure, the skin flushes and pales with each cycle of the heartbeat ; the flush is a systolic, and the paling a diastolic, event. Obviously, the phenomenon consists in alternate filling and emptying of

those vessels, which ordinarily give rise to the colour of the skin. In certain parts, notably in the skin at the base of the nail, in the lip, and less clearly in other places, human capillaries can be studied under the microscope and the flow of blood watched in them. The view is much facilitated by covering the integument with a highly refractile oil and by removing its superficial layers, as by blistering. Such examinations have provided conclusive evidence that the vessels mainly responsible for colour form the plexuses of minute venules in the superficial layers of the skin, and that the capillaries proper, the anatomical capillary loops of the papillæ, contribute little. The vessels concerned, and the manner in which they are involved, in capillary pulsation, were closely examined by a number of workers, including Boas, Sumbal, and myself; and it is now known that so-called "capillary pulsation" in the skin is mainly an affair of the venules. The venules in the cheeks of patients suffering from aortic regurgitation can sometimes be seen to pulsate under gentle pressure without the aid of lenses. In my clearest microscopic preparations of the living skin of finger and arm, pulsation occurring in the venules was repeatedly witnessed; and close attention in various circumstances allowed the pulse to be traced from arteriole right through the capillaries and minute collecting venules into the deeper lying venule plexus. The pulsing was seen to be an abrupt movement in the normal direction of the blood current and never in the reverse direction, being manifestly transmitted from arteriole to venule through capillary channels. Capillary pulsation is not due to expulsion of blood from the venules by lateral displacement when the arterioles expand; it is not ordinarily contributed to by the pulse passing directly from arteriole to venule through the special anastomoses described by Hoyer, though very possibly these anastomoses do contribute where they are numerous in special places like the palmar surface of the finger. Pulsation is often more easily seen under the microscope in venules than in capillaries, because in the former pressure is less and their walls are under less tension; thus the veins under slight external pressure pass from a position of actual collapse to one of expansion with each beat of the heart; rhythmic expansion and collapse of the capillaries is not often seen, but rhythmic change in rate of flow is always present though, owing to the

rate of flow in these vessels, it may be very difficult to detect. So much for what is visible ; we turn to consider the cause of the phenomenon.

It would not be true to say that at the time the following investigations were made, capillary pulsation was regarded as decisively indicating reflux at the aortic valves ; but it would certainly be true to say that capillary pulsation was hardly ever considered or discussed except in relation to the diagnosis of aortic regurgitation. Educated to look for and to be content to find " capillary pulsation " in cases of aortic reflux, for many years I remained satisfied with knowledge that there is this association. Although I became aware that Glaessner had found the same phenomenon in the flushed skin of Graves' disease and in some other conditions, it was not until years had passed, and occasional cases forced themselves upon my notice, that I began to realise the frequence of this phenomenon in patients suffering from a variety of maladies, and to become more interested in its mechanism in these. It had been impressed upon me too in earlier work that among phenomena originally described as physical signs of disease, and consequently regarded as essentially morbid, many have afterwards been recognised to occur in perfectly healthy people (*see* page 61) ; so I wondered if capillary pulsation was in fact essentially morbid or whether it might not be exhibited often by healthy men ; enquiry very quickly showed this to be the case. Thus it became apparent that, setting on one side for the moment the occasional instance of most vivid pulsation, obvious and slight pulsation cannot be specifically associated with one disease or several, but is displayed by many diseased and by many healthy people.

There is a method frequently employed and one that has high value to clinical science ; it has been described under the term " collective investigation " in the opening chapter of this book. In an instance like the present one, the method is employed in the search for the immediate cause of a phenomenon. We seek first of all one factor common to all the circumstances in which that phenomenon is known to occur. If we can find a single and adequate factor we may rest satisfied ; but from time to time we may be driven to accept the interrelation of two factors as alone satisfying. Thus, since capillary pulsation demands a pulse and also patency of the vessels concerned, it might come

to be expedient to regard as its cause, a pulse of amplitude adequate to penetrate vessels in their existing state of patency or, conversely, vessels sufficiently dilated to permit the prevailing pulse to pass. It will be perceived that these statements of immediate cause approach, if they do not actually attain, inevitability, in that they are almost equivalent to definitions of capillary pulsation. That does not detract from their value; the act of accurately defining, though it may be equivalent to the discovery of the immediate cause, will often prompt the next step or will at least present the problem to us with unmistakable clarity. In the present instance the attempt to define led the investigation in the direction of efforts more clearly to evaluate the respective parts played by pulse pressure and vasodilatation in capillary pulsation.

Because of its association with aortic disease, in considering capillary pulsation the emphasis had come to be laid upon pulse pressure, the large pulse of aortic disease being thought to be primarily responsible for the appearance of the sign. When cases of capillary pulsation were grouped for investigation and blood pressures were systematically taken, it soon became obvious that these could not be held regularly accountable. Capillary pulsation was found to occur in the presence of quite normal pulse and blood pressures. It could be produced in the hand of any young person by soaking the hand in water at 45° to 47° for a few minutes. Interestingly enough it was found to decrease in frequence, and in extent and intensity, with advancing years, a fact subsequently suggesting that the vessels in general dilate more readily or farther in youths than in older subjects. Greater security was given to the conclusion that a purely local vascular change, without possibility of change in the general circulation, suffices, by observing the effects of quite local heating. Heating no more than the tip of a finger in hot water, or heating the skin by means of a concentrated beam from a lamp over an area of but a few square millimetres, was seen to give in normal people distinct pulsation confined to the area heated. The pulsation was seen in flushed skin immediately surrounding small cuts and scratches, and in the fresh lesions of acne. In none of these last instances could changed pulse pressure be thought responsible.

Hand-in-hand with the demonstration that the capillary pulse can occur with normal pulse pressures came a growing conviction that it is associated usually or always with vasodilatation. Vasodilatation was common to all the instances just cited and these same observations helped much to define the order of vessel involved. Considering the small area of skin to which pulsation might be confined the vessels involved could be no greater in size than such arterioles as are to be found in the skin itself. It should be stated that simple dilatation of the vessels that give skin colour would not suffice, for capillary pulsation was not to be found in highly coloured skin that was cool or cold. The skin displaying capillary pulsation is always spontaneously warm and the arterioles supplying it are always widely opened up. The evidence already given that vasodilatation is concerned, harmonised with Glaessner's views, especially upon Graves' disease—in which however pulse pressure is increased—that vasodilatation may contribute. The same explanation would fit the flushed skin of fever (Quincke) and many other instances ; thus, personal observations had shown manifest capillary pulsation in the flushed facial skin of a blushing girl, of a case of cervical sympathectomy, and of normal subjects after inhaling amyl nitrite. These observations taken together formed a body of irresistible evidence. It is easy enough now that it is before us to wonder how the obvious factor of vasodilatation could have remained so long neglected ; yet this neglect was perhaps natural in the days when attention was concentrated upon aortic regurgitation. Once the scope of the enquiry was widened, once observation became systematic, and especially when, as a control, the skin of normal people came under close scrutiny, it was inevitable that the conclusion should become established that capillary pulsation demands dilated arterioles. But would this same explanation also fit the capillary pulse of aortic disease ? Or should we be forced to the view that in this instance it is the result purely of abnormal pulse pressure, and in others purely of unusual vasodilatation ?

The problem was finally pursued in cases of aortic regurgitation itself. An investigation of pulsation and skin temperature soon showed in these too that spontaneous capillary pulsation does not occur unless the skin displaying it is warm or hot. Often the facial skin of these patients was found to vary from part to

part ; the display of capillary pulsation varied correspondingly. The accompanying table clearly illustrates this relation in a case of free aortic regurgitation, the temperatures being ascertained by a thermocouple (Fig. 26). Similar statements apply to the hands ; if these were cold, it was useless to look for the pulsation in them. The relation to bloodflow as indicated by temperature was quite clear ; and in a case capable of showing vivid pulsation

| | Capillary pulse | Temp. (cent.) |
|---|---|---|
| Lobe of right ear | none | 23·4 |
| Bed of finger nail | none | 26·8 |
| Side of nose | none | 26·8 |
| Pad of finger | none | 28·1 |
| Pad of big toe | none | 28·1 |
| Heel | none | 28·5 |
| Right cheek | slight | 28·9 |
| Pad of big toe after massage | distinct | 31·2 |
| Forehead | very distinct | 32·0 |
| Left cheek | very distinct | 32·6 |
| Right cheek (later) | very distinct | 33·6 |
| Lower lip, facial mucous membrane | vivid | 34·7 |
| Lobe of right ear after massage | vivid | 35·5 |

any grade of pulsation could be provoked in the hand by soaking it in water of suitable temperature. Thus cases of aortic regurgitation fell into line with remaining instances of capillary pulsation ; in both types the relation between the phenomenon and the state of the arterioles was easily demonstrable. It could also be shown without difficulty for aortic regurgitation and comparable cases that capillary pulsation may be independent of abnormal pulse pressure. To illustrate, a man exhibiting free aortic reflux gave blood pressure readings in the brachial artery of 135 systolic and 35 diastolic ; a pneumatic cuff was placed on the upper arm at a pressure of 90 mm. Hg and the veins below allowed to become fully engorged. In these circumstances the pulse pressure in the arteries of the forearm could range only between the extreme limits of 135 and 90 mm. ; yet capillary pulsation was still distinct in the finger tips. There was also the very convincing instance of high pulse pressure in the case of arteriovenous anastomosis of femoral vessels described on page 46, where obliterating the common femoral vessel cut out the leak and restored the pulse pressures to normality ; yet capillary pulsation was equally vivid in the two sets of circumstances. Here was proof that capillary pulsation may not depend on the high pulse pressure with which it is associated.

But in the end it could not be said that the high pulse pressure of certain diseases does not contribute, or that vasodilatation is the single factor concerned. If cases of aortic regurgitation displaying pulse pressures of different amount were chosen, and the arterioles in the hand of each were brought into more or less the same state of dilatation by soaking in water at about 40°C., the intensity of the capillary pulse could be shown to vary distinctly with the size of the pulse. The following evidence is even more convincing, because only a single individual was

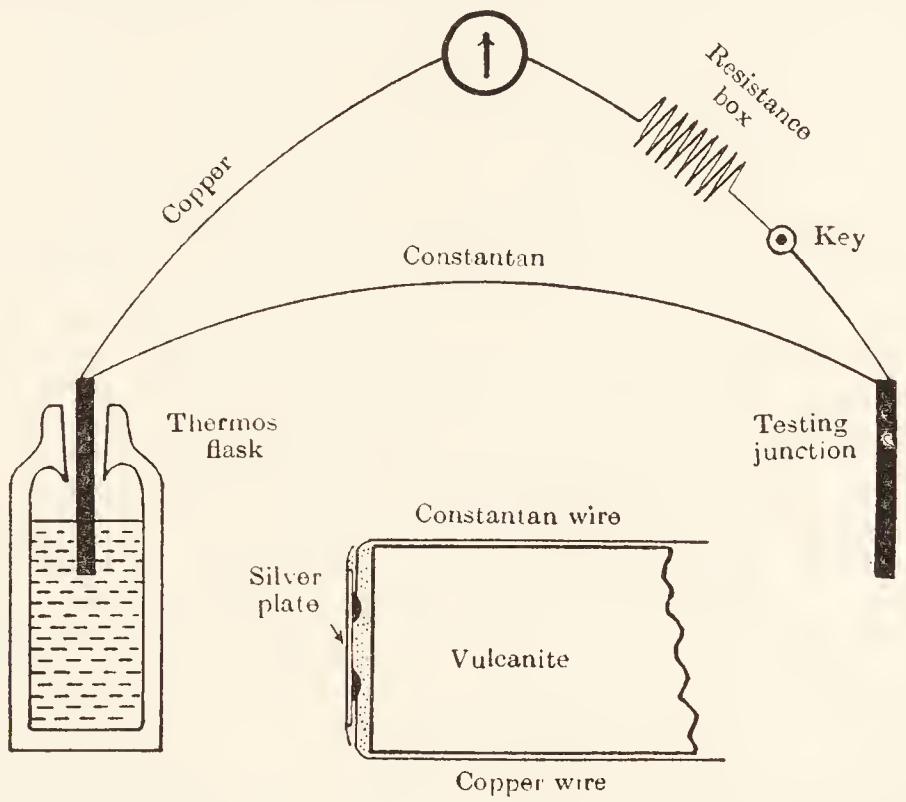


FIG. 26. A simple apparatus, consisting of two thermoelectric junctions, one used to test, while the other is kept at constant temperature in a thermos flask. The junctions are joined in series with a simple galvanometer, the deflection of which is used as a gauge of temperature difference between the junctions. The inset illustrates the construction of the actual thermal junction carried on the end of a vulcanite rod. This apparatus was devised for studying skin temperatures, in connection with the observations on capillary pulse here described, and has since been in constant use in other investigations.

concerned and pulse pressure alone varied. It was a case of syphilitic aortic disease, in which the mouth of the innominate artery was presumably narrowed, for the pulse pressure in the right arm was 56 and in the left 114 mm. ; despite this difference the bloodflow, measured by the method briefly described on page 47, was found to be equal in the two arms ; capillary pulsation was present in the skin of both arms, but it was more vivid on the left side.

The presence of actual vasodilatation in the facial skin in cases of aortic regurgitation was shown by closely comparing

the temperature of the skin with that of normal subjects under like conditions of environment; in the aortic cases it was higher.

To sum up, in aortic disease or in other states capillary pulsation never occurs unless the arterioles are well open; it may be said of most cases that this certainly means actual vasodilatation, namely, that the vessels are wider than they would be in healthy people under similar conditions; but it is probable that where pulse pressure is excessive, a capillary pulse will manifest itself when the arterioles are well open, even though actual vasodilatation cannot be claimed. Finally, if we are to state the cause of capillary pulsation, the statement will be that it occurs when the arterioles are sufficiently dilated to permit the prevailing pulse to pass, thus throwing the emphasis on the state of the arterioles. What induces the arterioles to open up in aortic regurgitation and in arteriovenous anastomosis is unknown; the dilatation compensates perhaps for the low mean arterial pressure prevailing usually in these diseases.

A final comment closes this chapter. It has been a habit of those working among sick people to correlate "physical signs" observed, so far as possible with specific states of disease. It has been a very natural tendency because a chief end point in view is diagnosis of these states of disease; but such correlations unduly stress the association discovered and may result in more general, and therefore more important, correlations remaining concealed. The capillary pulse is a case in point; in practice its presence very rarely leads to the diagnosis of aortic reflux; it never should be used in finally arriving at the diagnosis; but its association with defect of the aortic valves, has resulted in a much more significant relation being overlooked. Capillary pulsation is very often valuable in identifying a dilated state of the arterioles, local or general, and for this purpose it should mainly be used. Another slightly different but equally instructive example of how the most important significance of a phenomenon can be overlooked, because that phenomenon comes to be identified too closely with diagnosis, will be found in the example of "erythralgia," given in Chapter 14. Further comments referring to the general point of view are included in Chapter 15.

NOTE.—Relevant references and the original observations will be found in *Heart*, XI, *p.* 151.

# CHAPTER 7.

## TRIPLE RESPONSE OF SKIN TO INJURY.

### RESPONSES TO STROKING.

In 1915-16, while investigating with Cotton and Slade the reactions of the skin of certain patients to the stroke stimulus, interest was aroused not only by the blanching of skin in response to light strokes (Chapter 5) but equally by the red reactions to heavier strokes. Usually a firm stroke with a bluntly pointed rod of about 5 mm. diameter, made on the white skin of trunk or limb, results in a red mark of corresponding breadth and having sharply defined margins. This red line appears usually in a few seconds, develops fully in about 30 seconds, and fades away at very varying times from 2 to 30 minutes, or sometimes much longer. Bright red in colour at its first appearance, it soon acquires a slight but distinct cyanotic tint. If the stroke has been heavier, to the point of being painful, the red line often shows a little swelling subsequently; and it is usual for the skin surrounding the area stroked to develop what has come to be called the "flare." This flare appears usually in about 20 seconds or a little longer; it is of very bright tint, but fades and disappears much more quickly than does the red line. The flare everywhere closely surrounds the red line, but the boundary between the two is distinguishable from the time when the red line assumes its cyanotic tint, if not earlier. The flare spreads to a variable distance, usually one or more centimetres out into the skin; its margin is ill-defined and irregularly crenated; the flare though uniform in tint is patchy in intensity. At the time, interest centred upon the kind of vessels involved in these red reactions, and a first consideration was whether the flare was merely an extension of the central red line, or must be considered to result in a distinct way. The brightness of its colour, the lack of

uniform density or clearly defined margins, and the time of its appearance and fading suggested to us, as certain of these features had previously suggested to Müller, that the red line and the flare are distinct vascular effects.

## VESSELS INVOLVED.

We argued that the red line and the flare surrounding it must both be due to engorgement of the minute vessels of the skin; and that this engorgement might be brought about either by the active relaxation of arterioles or of the minute vessels, or by a constriction of venules. In the case of the flare we could not suppose the venules constricted, owing to the fresh colour of the skin and the maintenance of this arterial tint. But the freshness of colour, its mottled density and crenated margin suggested to us, as to Müller, that the flare is arteriolar in origin and that the order of vessel is displayed by the size of the individual crenations. In the case of the red line, its assumption of a cyanotic tint seemed clearly opposed to its origin in arteriolar dilatation. The red line following heavy, and the white line following light, pressure are alike in form and in spatial relation to the stimulus; relaxation and constriction, respectively, of the smallest vessels would account for the contrast of colour, while the involvement of one and the same set of vessels in the primary change would explain the constant form of the reaction, and its confinement to the area stroked. Another powerful argument, for the origin of the red line in an active change of the minute vessels, was that previously used for the white one, namely, the crispness of its margins; there was no apparent reason why, if the minute vessels were passively dilated, the blood should not flow out into neighbouring and anastomosing vessels of a like order.

Consideration enabled two tests to be devised; these were found sharply to distinguish between the redness of the flare and that of the line, and brought firm support to the preliminary view of their individual mechanisms. Firstly, a suitable skin is firmly stroked vertically with a blunt point, and the red line with surrounding flare obtained. A stroke is now drawn horizontally across this reacting skin, a stroke of a lightness sufficient to induce the white reaction. This white reaction abolishes the corresponding area of flare, but is without effect upon the red

line. This differentiation, sharp as it proves to be, was anticipated. The white reaction was held to signify active contraction of minute vessels ; such contraction would abolish any passive dilatation of these vessels consequent upon arteriolar dilatation, but it would not abolish a relaxation of the minute vessels supposedly arising out of some paralytic condition of their own walls. Secondly, if upon skin of the arm known to yield red line and flare, an adequate stroke is made after the circulation to the limb has been stopped by pneumatic pressure, the flare fails completely, but the red line appears slowly and distinctly. The flare fails because in these circumstances widening of the arterioles cannot increase the pressure in the minute vessels of the corresponding area of the skin ; the red line appears because the normal tone of the minute vessels relaxes and the vessels fill with blood from those with which they anastomose. The test may be carried out with the arm hanging by the side and without previously depleting it of any of its blood ; the red line then appears in much the same time and with much the same intensity as it does on the skin to which the circulation is free.

### RELATION OF WHEAL AND VASCULAR REACTION.

Evidence having first been obtained to prove that there are two vascular reactions, one of the minute vessels and one of the arterioles, attention was turned at a later date to the wheal. The wheal is part of the full response ; it is almost invariably associated with a conspicuous local reaction and with a widespread and brilliant flare. It develops to its height about 3 to 5 minutes after stroking, and is at first red ; but if it rises a millimetre or two above the skin it often becomes tense enough to blanch, and the sharply defined ridge of pale swollen skin is then very prominent. By this time it was known, as the result of our own work and that of Ebbecke, that the full response of local reddening, wheal and flare, can be obtained in a number of normal subjects, especially in the young, or by using strong or repeated strokes. Thus this full response, which was considered originally as a complete departure from normal under the name "urticaria factitia," came to be regarded as merely an exaggerated physiological response ; and in parenthesis it is noteworthy how often such a sequence of conclusion has been

repeated. But the fact that the wheal, with all its associated vascular phenomena, is a normal response of skin to injury, made a clear understanding of its mechanism all the more important. Attention was first concentrated on the relation of the wheal to the vascular events in urticarial subjects, and it was shown that the gathering of fluid in the tissue is not the simple result of increased filtration pressure, or of such increased permeability of the vessel wall as might be supposed to result from distension, but that it is necessary to suppose that the wall of the minute vessels undergoes an intrinsic change, its permeability increasing independently of any associated stretching. The evidence for this statement, obtained from urticarial subjects, may be given briefly. If the venous return is obstructed by pumping up a cuff on the upper arm to 60 or 70 mm. Hg, the vessels of the forearm become much dilated and the differential pressure between their contents and the fluids of the surrounding tissue spaces increases greatly; yet in these circumstances a stroke on the skin of the forearm was found to produce a wheal of reduced size, and not of increased size as would be expected if whealing depended mainly upon stretching of vessel wall or filtration pressure. Next it was found that wheals will develop if the distension of vessels and high differential pressure natural to whealing are largely counteracted and prevented. This was done by the simple expedient of throwing pneumatic pressure upon skin immediately after stroking it, and watching the effect upon the developing vascular dilatation and wheal. It was ascertained that wheals will develop in skin supported in this way by external pressure as high as 50 mm. Hg. Now when such supporting pressure is a little higher, is in fact just enough to prevent whealing, it is also sufficient to prevent the flare appearing, and the red line develops faintly or not at all; that is so because the pressure developed in the minute vessels of the reacting skin is no more than 70 or 80 mm. Hg. Such pressures are also developed in the vessels of the red line produced by stroking normal skin that does not wheal. Thus, although the differential pressure is not very dissimilar in the case of normal and abnormal skin, the former does not wheal, but the latter wheals even when the differential pressure is artificially reduced to less than half its ordinary value. It is therefore manifest that differential or filtration

pressure is not a chief factor. The wheal forms because there is a change in the vessel wall; independently of mechanical factors, it becomes much more permeable. It became clear from simple calculations that a high percentage of all the fluid parts of the blood entering the minute vessels must pass out through the leaky vessel wall; and the fluid of the wheal when sampled was found to clot and to contain 67 to 84 per cent. of the blood proteins. But given increased permeability, thus so clearly evidenced, then the rate of oedema formation is influenced greatly by the rate of bloodflow. Wheals form prominently when there is a conspicuous flow of blood and rise of temperature to the part; a wheal never forms while the arteries to the limb remain occluded. The chief conclusion reached was that increased permeability and dilatation of vessel are independent. At a later date this conclusion was abundantly confirmed in experiments with Grant, which demonstrated that owing to a change termed "refractoriness" (*see* page 82) the full vascular reaction may be caused to appear without its usual companion the wheal, a clear instance of their dissociation.

## THE TRIPLE RESPONSE.

The investigations had now come to the point where it could be said that the full response to the stroke consists of three associated but independent reactions, namely, a local dilatation of minute vessels, an increase in the permeability of their walls, and a widespread arteriolar dilatation. To this complex three-fold reaction it was convenient subsequently to give the name "triple response."

At this stage Grant and I began our work together of exploring this triple response further. Very early in our enquiries we came to understand what had not previously been realised, or realised at anything like its full significance, namely, that this triple response is not peculiar to the stroke stimulus, but that reactions presenting no essential difference can be obtained by means of many different forms of physical injury such as cutting, scratching, burning, freezing, and by a variety of irritant substances placed upon or introduced into the skin. One of our cares was to institute a very searching comparison between the response to two dissimilar forms of stimulation, the one physical, the other chemical. Remarkable resemblance was found not only between

the responses and their time relations (as shown by the accompanying table), but in their behaviour under a great variety of conditions. There were but occasional and minor differences such as would naturally arise from the manner of applying the

| Zero time. | Stroke. | Histamine puncture. |
|---|---|---|
| After 20 sec. | red line begins | red spot seen. |
| ,, 30 sec. | flare begins | flare begins. |
| ,, 70 sec. | wheal begins | |
| ,, 80 sec. | | wheal begins. |
| ,, 3 min. | wheal almost full and pink | wheal almost full and pink |
| ,, 8 min. | wheal pale | wheal pale. |
| ,, 47 min. | wheal pale and diminishing | wheal pale and diminishing. |

In a susceptible subject the skin was stroked, and simultaneously it was pricked through a drop of 0·1% histamine phosphate solution. The table gives the times at which the chief events of the two reactions occur. These times are very similar in the two instances.

stimulus, and these were easily to be explained. The fact that we made a significant choice in selecting histamine for use in a final and intimate comparison is not immediately relevant ; but it will be commented upon later. In attempting a full comparison it became necessary closely to investigate the influence of different nerve injuries upon the various parts of the triple response. Müller, Breslauer, Ebbecke and others had published from time to time evidence that, in response to this stimulus or to that, part of the vascular reaction fails in various cases of nerve injury. But it was unclear at the time if the several vascular reactions that had been investigated were in fact related. It was imperative to our work that these questions should be resolved. By making use of a variety of nerve injuries, the conclusion was reached that the flare produced by stroke, scratch, burn, or by the introduction of histamine, is constant in its nature, and depends in each instance upon the integrity of the terminal parts of the peripheral nerves. There was enough evidence upon which to proceed, though the solidarity and width

of the present day conclusion, discussed with its evidence in Chapter 9, depends much on later observations, which definitely pinned the reflex to the axons of sensory nerves. We confirmed and rendered general the statement that, unlike the flare, the red line and the wheal are independent of nervous mechanism, central or local. This incidental work upon the nervous apparatus concerned had two effects upon the general progress of the investigation. Firstly, it allowed a more precise definition of the triple response, which now could be stated to consist of:—a local dilatation of the minute vessels, an independent increase in the permeability of these vessels, a widespread arteriolar dilatation, dependent (and alone dependent) upon a local nervous reflex. It thus emphasised the complexity of the response. Secondly, it hardened the conclusion at which we were arriving, namely, that the triple response is not peculiar to this or to that stimulus, but is a fundamental response of the skin to injury.

We may pause here to state that this same process of analysing the reactions of the skin to injuries has continued, and other responses, such as those to freezing, to galvanism, and to faradism, have since been brought into line; but the central conclusion has remained unaltered. There is here an illustration of method; the net being cast widely, each captive is subjected first to minute dissection; but when all is done and appropriate comparisons have been made and small differences noted and explained, the whole mass of information begins to fall into simple patterns, and by inductive reasoning important generalisations begin to emerge.

## RELEASE OF A TISSUE SUBSTANCE.

As soon as the conclusion was firmly established that stimuli, physical and chemical, of quite distinct kinds are capable of yielding in a surprisingly uniform manner a very complex response, comprising actions on the vessel wall and on the nerve endings of the skin, the urge to identify some common underlying factor of causation, interposed between apparent stimulus and reaction, became insistent. One of the most obvious possibilities, and one which suggested itself simultaneously and independently to Ebbecke and ourselves, was the

liberation of a substance from the tissues by injury ; for it was manifest that almost every one of the agencies known to produce the triple response, if acting in greater intensity, would kill the cells of the skin. For a long time it seemed as though the enquiry would end at this point in the expression of a hypothesis ; but constant pondering of the problem at last showed a possible way to more certain knowledge. The idea to be tested was that a definite substance released could act upon the vessels and nerves concerned and produce each of the three composite parts of the triple response. Could we obtain evidence of such a release ? It was seen that this might be done if by good fortune the substance released happened to be a stable one. When histamine is pricked into the skin of the arm, it produces the characteristic triple response, including a widespread and vivid flare several centimetres in diameter. As time passes this flare gradually disappears, becoming less bright and shrinking at its margins ; within 9 or 10 minutes it has decreased very greatly. It was found that if histamine is introduced simultaneously into the two arms, and the circulation to one is stopped for 9 or 10 minutes, the flare on the other will much diminish before the former arm is released. This arrest of the bloodflow to the area postpones the fading of the flare ; and it postpones it approximately by the time during which the bloodflow remains arrested (Fig. 27A). Now the meaning of this delay is manifest. The histamine punctured into the arm continues to act and maintains the arterial flare as long as it remains there. When the circulation is free the histamine is gradually absorbed, but while the bloodflow is held arrested this absorption is at a standstill. The interpretation is simple and possesses little intrinsic importance ; its importance appears in its application. When we came with keen expectancy to test the matter, it was found that the arrest of bloodflow to the skin delays the fading of the flare around a stroke in exactly the same way as it does that provoked by histamine (Fig. 27B). This was a crucial test, which placed the direct action of the mechanical stimulus out of court, and proved an intermediate chemical stimulus to be the direct cause of the stroke flare. So much for the flare, which provided the first clear evidence ; but the response consists of three parts. Does the local vascular dilatation and does the increased permeability also depend on the released substance ? The

answers to these questions came later and in the following way. If histamine is punctured into the skin and the circulation to the limb is stopped, a circular spot of redness appears upon the skin, as the vessels directly influenced lose tone and fill with

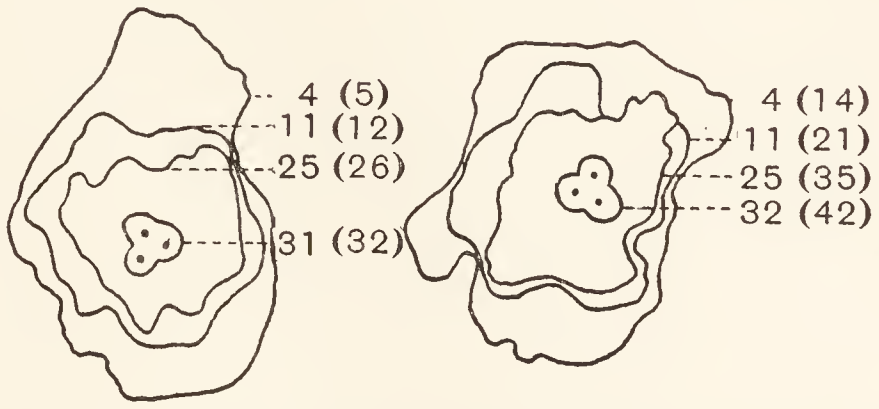


FIG. 27A.—( 1/2 nat. size). In this and the succeeding figure, the left diagram corresponds to the left arm area, and the right to a symmetrical right arm area of skin. The vessels to both arms were occluded ; a group of three histamine punctures was put down on the right forearm 1 minute after the occlusion and on the left forearm 10 minutes after the occlusion. The circulatory arrest was continued in each to the 11th minute, when both arms were released. The two flares were outlined at fixed times after the release and these times are expressed in minutes against the corresponding contours. The numbers in brackets represent the corresponding times elapsing after the stimuli were laid down. It will be gathered that after release the right arm flare fades away at the same rate as the left arm flare ; but that the fading, timed from the stimulus, is delayed 9 minutes on the right arm.

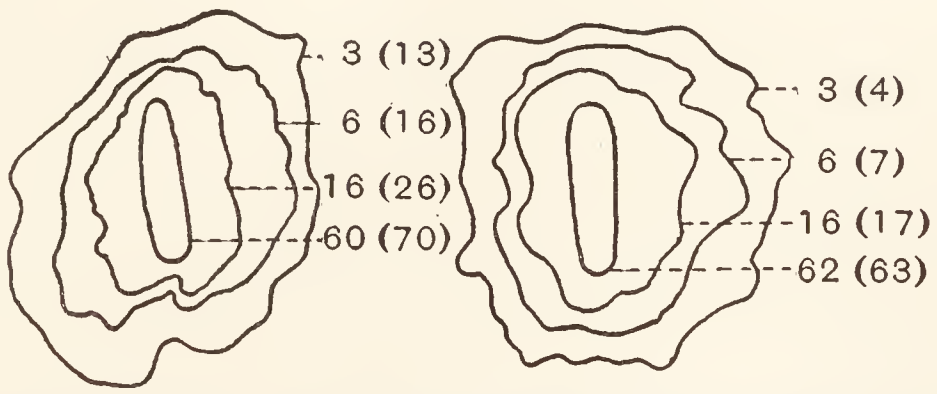


FIG. 27B.—(1/2 nat. size). Urticarial subject. The vessels of the two arms were occluded. One minute later the left forearm was stroked and at the tenth minute the right arm was similarly stimulated. The contours of the flares, as these appeared and faded after the release of the circulation to the arms at the 11th minute, are shown.

blood. This circular spot has a relatively crisp margin, and it enlarges very slowly but definitely in size in the space of 10 minutes. This spread of the local reaction during circulatory arrest obviously results from diffusion of the histamine outwards. When in a patient ordinarily giving a strong triple response to

stroking, the skin is firmly stroked and the circulation is kept stopped, the margins of the red line, which develops, move outward in the same way and at a similar rate as do those of the red spot of histamine. Here evidence was found in a simple observation that the occurrence of local vasodilatation to stroke depends upon a diffusible substance. It was easy to show that a similar conclusion applies to the increased permeability, for the wheals developing in response both to histamine and to stroke, extend to the outer margin of the local red response as this is seen in its full extension immediately before release; that is to say, the diameter of the developing wheal is greater if the circulatory arrest lasts many minutes, thereby allowing histamine or injury substance a preparatory period for diffusion. Thus evidence was obtained that each part of the triple response is the indirect result of the stroke, and that all three depend upon an interposed chemical factor.

In regarding the work upon vascular responses to injury from the historical standpoint, it is to be recognised that knowledge came in two chief steps. Firstly, enquiries, which have just been outlined, led to the conclusion that the triple response to injury results from the release of a substance in the skin. Secondly, and in natural sequence to the first, which gave the necessary confidence to proceed, enquiries about the substance led to beliefs as to its nature with which we are about to deal.

## NATURE OF THE SUBSTANCE.

It will be of interest to trace to its source the idea as it came to us that histamine or a histamine-like substance is concerned in the triple response to injury. When Grant and I began our work together we considered what chemical substance, of those already known to produce whealing, should be used in our tests; we had a choice between a number including histamine, peptone, atropine, and morphine (Sollman and Pilcher). Our choice inclined towards histamine because it was a pure substance of known chemical constitution, because it was known to act in very high dilution (Eppinger), and because Dale and Barger had actually isolated it from mammalian tissue. Knowing his work upon and particular interest in histamine, we consulted our colleague Dale and he made for us the same choice. It should be

recognised that when we began to use histamine upon the skin, the idea that this or a related substance might be responsible for urticaria factitia was not under consideration ; the idea could not be in mind, except in the vaguest way, until evidence was forthcoming for the preliminary notion that some chemical substance intervenes between physical assault and reaction. Looking back, therefore, it would seem as though the selection of histamine for our tests was a happy accident. It may have been so, and yet I think the choice was not wholly accidental. In scientific work the atmosphere often becomes gradually prepared for a given speculation or conclusion ; a stage is reached when a conclusion is approaching inevitability, although this cannot always be seen till afterwards ; it is only a matter of time and the conclusion will be formed. The truth of this statement is often illustrated by the almost simultaneous statement of the same conclusion by men working independently and providing distinct lines of argument. This was so in the case of histamine ; histamine was so to speak in the atmosphere, when questions relating to injury were discussed. The work of Dale with Laidlaw and Richards, and of Cannon and Bayliss, and the suggestions arising out of their observations, was bringing histamine into the foreground of discussion on shock, resulting either from anaphylaxis or wounds. Ebbecke for different reasons from our own actually came independently to the same conclusion as ourselves, and a little earlier in point of time. As has been indicated already, our own starting point was in the evidence for an intervening substance; this led on at once to the question of its nature. It was thus that histamine came under suspicion as the agent responsible for the local vascular reactions to injury, a suspicion supported by the following observations.

In examining the behaviour of wheals in a variety of circumstances, it was found, as previously stated, that no trace of whealing occurs in skin to which the circulation has been stopped, but that the wheal develops soon after the circulation is released again. It was noticed repeatedly, however, that such delayed wheals are often of reduced height and sometimes fail to appear. Using the histamine stimulus, attention to precise circumstances taught that whealing can be prevented by arresting the flow for a long enough time and by keeping the skin unusually warm. This phenomenon interested and puzzled us ; and we were

brought ultimately to conclude that the action of histamine on the permeability of vessels is peculiar. When the wheals form permeability is increased, but after a time, although the vessels remain dilated, it declines again. This is known not only for skin to which the circulation has been stopped, but for that in which it is free; thus Ebbecke injected trypan dye into the bloodstream and found it to appear in wheals that were developing, but not in wheals already formed. When the circulation has been stopped until this phase of lowered permeability has set in, it is natural that no wheal should appear at the circulatory release; but this circumstance allows the state of the tissue to be tested, and it is then found that wheals will not form in response to histamine freshly introduced. The vessels have entered the very interesting state which Grant and I called "refractoriness"; this state lasts many minutes, recovery from it is gradual. Being unable to ascribe this condition of refractoriness to any simple mechanical disturbance of the vessels,* the view was taken that it results from a change in the vessel wall consequent upon the action of histamine upon it. Enquiry now showed, however, that stroke wheals behave in the same fashion; skin that has been stimulated and kept from whealing will not wheal to a fresh stroke stimulus. Moreover the stroked skin becomes refractory to histamine and the histaminised skin becomes refractory to stroking. Thus the two are interchangeable. These experiments afforded presumptive evidence that underlying refractoriness there is one chemical reaction; and brought us more seriously to contemplate the idea that histamine or a substance closely resembling it, may be the actual substance liberated in injured skin.

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* We were careful to exclude stasis in the vessels. Hoff (*Zeitschr. f. d. ges. d Med.*, *Vol.* LVII, *p.* 253) three years later described experiments on urticaria factitia and recorded again the failure of a wheal to occur where the skin has already been whealed. Hoff believed that the first wheal fissures the skin and that these fissures rapidly conduct away the fluid, which would otherwise form the second wheal. The present note is rendered necessary by Krogh's statement ("*Anat. and Physiol. of Capillaries*," 2nd Ed., *New Haven*, 1929, *p.* 331) that he unreservedly accepts this interpretation of Hoff. I venture to think that Hoff would not have come to his conclusion had he been conversant with previous work; for Grant and I first demonstrated refractoriness in skin that had not been allowed to wheal previously. Hoff's own observations are in themselves quite unconvincing of the view he adopts. The Duke-Elders (*Proc. Roy. Soc.*, *B.* CIX, *p.* 19) have recently shown that refractoriness is displayed by the vessels of the iris and that then transudation of fluid into the anterior chamber of the eye does not occur as usual to stimulation, a decisive evidence in support of our view.

Repeated attempts were made to ascertain if a histamine-like substance is present in the fluid obtained from the wheals of urticaria, by testing the reaction of the guinea-pig's uterus to this fluid. Although it was found that the uterus contracts in response to the fluid, the result could not be used in support of our hypothesis, because of our inability to obtain from the same subjects and by similar methods, blood plasma that would constantly yield a smaller contraction or no contraction. A few years later, however, Miss Harmer and I demonstrated that if the skin of a subject, presenting urticaria factitia, is whealed over considerable areas of the trunk, a general vascular reaction happens too, comprising flushing of the face, warming up of the skin generally, a fall of blood pressure, and a rise of pulse rate. This general reaction is identical with that obtained by injecting a small quantity of histamine subcutaneously, and its time relations are similar. This result has since obtained an important confirmation from Kalk* who found that stroking, like histamine, causes a secretion of gastric juice that is uninfluenced by atropine. The isolation of histamine in quantity from the lung by Best, Dale, Dudley and Thorpe, was another important step, and this led to the preparation of alcoholic extracts of skin. With Harris,† I was able to show that these skin extracts produce the triple response when pricked into human skin; and Harris, continuing the observations, showed that they give the same responses of uterus and blood pressure as does histamine. He found too that the active substance is present in much greater concentration in the superficial or epithelial, than in the deeper layers, of the skin.

These are the main facts and arguments upon which the original conclusion was based, or which have since given it greater warrant, that injury releases from the tissue cells a histamine-like body or histamine itself, and that this "H-substance" as it has been termed is responsible for the vascular reactions comprising the triple response in all circumstances in which it is seen.

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* Kalk. *Klin. Woch., Vol.* VIII, *p.* 64.

† Harris. *Heart, Vol.* XIV, *p.* 161.

## COMMENT.

The observations and experiments outlined in this chapter began in the study of red reactions of the skin to stroking, phenomena which, passing under such names as "tache cerebrale" had been regarded as significant of diverse diseases. Little was known of the mechanism of these red reactions to stroking, or of the whealing of the skin with which they are so often associated; the term "vasomotor neurosis" came to be applied to this and to other cutaneous happenings involving flushing, and served merely as a mask for ignorance. Deliberate study soon altered this situation and led to the conclusions that these phenomena are normal, or merely exaggerated, responses of the skin to injury, that the complete triple response is the common acute reaction to all forms of injury, and that it has underlying it the release of a substance natural to the skin. There exists in the skin a highly organised mechanism of defence against injuries, which may be summed up in the word *inflammation*. Although this term now has a much more comprehensive meaning, it was originally used to cover just those local processes that are considered in this chapter, namely, redness, heat, and swelling; it is these vascular manifestations comprised in inflammation that the investigations in their development have gone so far to explain. The investigation of the white line (Chapter 5) led us as has been seen to a fundamental revision of views then current of capillary function. The investigation of the red line broadened out and brought us to generalisations of wide, and still widening, significance in relation to the defences of the skin. A fuller view of its development will be gained from my book "*The Blood Vessels of the Human Skin and their Responses*," and illustrations will be found in Chapter 8. These are two unusually instructive examples of enquiries which, at the beginning, seemed to concern problems that might readily have been regarded as of limited or trivial interest, but which developed and grew, as such enquiries are apt to do, to unexpected importance.

There is another aspect of these investigations upon which comment may be profitable. An experiment of crucial importance to the development of these studies was that in which the fading of the flare was found to be postponed by circulatory

arrest. The principle involved in this test, has found repeated application in other studies. Occlusion of the vessels to a limb was afterwards used by Marvin and myself* in showing that a stable vasodilator substance is released in skin by antidromic stimulation of sensory nerves, and to establish a sharp distinction between this form of vasodilatation and that caused by stimulation of the nervi erigentes. A similar procedure was used to demonstrate that the sensation "itching" is commonly, if not always, due to H-substance released in the skin†. The effect of circulatory arrest in prolonging pain provoked by somatic muscle working without adequate blood supply was the starting-point of investigations leading to the conclusion that such pain and the pain of angina pectoris are due to an accumulation of muscular metabolites (*see* Chapters 10 and 11). Still more recently, in studying the burning pain of the skin in erythralgia, the opportunity of applying a similar test was deliberately sought, and a little manœuvering permitted it once more to be successfully used, as is described in Chapter 14. These are simple but useful illustrations of how one investigation may spring from, or be aided by, another with which it may seem to have beforehand little in common. Work upon one problem brings experiences that may be seen to be peculiarly fitted for use in the solution of a distinct problem; and the opportunity when seen is seized. Thus, they illustrate the advantage of continuous and systematic research in clinical science, and of working without being confined within the narrow boundaries of a single anatomical system.

Note. The full description of observations and experiments described in this Chapter will be found in articles by my collaborators and myself in *Heart, Vol.* VI, *p.* 227; *Vol.* XI, *p.* 119 and 209. References to authors other than those given in this Chapter will be found in these articles and in "*The Blood Vessels of the Human Skin and their Responses,*" *London,* 1927.

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* Lewis and Marvin. *Heart, Vol.* XIV, *p.* 27.

† Lewis, Grant and Marvin. *Heart, Vol.* XIV, *p.* 139.

# CHAPTER 8.

## EXTENSIONS OF WORK ON TRIPLE RESPONSE.

In the last chapter certain investigations are reviewed, which lead to the conclusion that the triple response is the common and characteristic response of the skin to acutely injurious stimulation; and it has been seen that this is the common form of response because it is determined by the release of a natural substance from the cells of the skin. The original work carefully explored the reaction to so many kinds of stimulation that it seemed to justify a conclusion by inductive reasoning, namely, that the triple response follows in a healthy skin when an injurious stimulus of any kind is of appropriate intensity; and, provided that histamine or like body has not been introduced artificially, it seemed to justify the second induction, namely, that when the triple response occurs it is always due to the release of H-substance from the cells. When this second generalisation was first put forward, it was done with a slight reservation, mainly because the response to faradism was imperfectly understood. But when the latter was further explored* it was found to fall into line, and the conclusion then came to be held without reserve.

The present chapter, while illustrating some of the ways in which the work on triple response extended, will begin by showing the value of a generalisation such as that just formulated and its impulse to further progress.

### ANAPHYLACTIC SKIN REACTION.

Shortly after completing our main observations upon the triple response of the skin to injury, our attention was turned to what has often been termed "protein sensitivity" of the

* Lewis, Grant and Marvin, *Heart*, *Vol.* XIV, *p.* 139.

skin. A man came under our care who had suffered from both eczema and asthma for many years and who also complained that he had been unable to eat or to handle fish at any time within his memory, owing to its producing swelling of any part of his skin with which it came in contact and, when ingested, a generalised rash over his body. He was found when tested to be very highly sentitive to fish, more particularly to herring ; the lesions could be produced very readily by placing a drop of highly dilute extract of herring on the skin and puncturing the skin through it with a sharp needle. Simple needle pricks, firm strokes, and puncture with histamine gave quite normal reactions. Cases of this kind were well recognised at the time and, as in those reported by Prausnitz and Küster and by Freeman, the sensitivity could be transferred passively to normal skin by injecting our patient's serum into it. Our particular interest in the case lay in our desire to ascertain if the reaction displayed to fish puncture was in fact identical with that with which we were already so familiar. Hare, who worked on similar lines and came to very similar conclusions, published his cases of horse and pollen sensitivity simultaneously with ours. When appropriate tests were used, there was no difficulty in showing that the response was three-fold, consisting of local vascular reaction, flare, and local œdema. Arrest of the bloodflow to the skin prevented the flare appearing, but displayed the local reaction to advantage ; if the arrest was long enough and the skin kept warm, little or no wheal formed. In Hare's cases actual refractoriness to histamine was recorded. When histamine and fish extract were punctured simultaneously into the patient's skin, the strengths being so arranged that similar whealing eventually resulted, the two reactions were found to run parallel at all stages, flushes and wheals appearing almost together and subsiding in much the same times. The two lesions were in all respects indistinguishable ; both were accompanied by itching. It was thus proved that the reaction to the noxious substance consists of the ordinary triple response, comprising the three independent effects described in Chapter 7. From this we were lead to the idea, applying the generalisation that the triple response is always produced through the same immediate mechanism, that the noxious substance introduced into sensitised skin does not act directly on vessels and nerves but damages the

cells of the skin and releases H-substance locally, this released H-substance now giving rise to the ordinary triple response. Strictly speaking, upon the basis of the evidence presented, this conclusion was applicable only to skin sensitivity; but its possible bearing upon the general problem of anaphylaxis was so obvious that this aspect seemed also to call for comment. Even if it is believed that "protein" sensitivity does not illustrate a phenomenon identical with the anaphylactic reactions that have become models in animal experiment, it is certainly not to be doubted that it holds much in common with them.

The resemblance between anaphylactic shock and shock produced by the injection of protein cleavage products was first pointed to by Biedl and Kraus, and later emphasised by Dale and Laidlaw, who particularised histamine in this respect. The resemblance in detail between anaphylactic and histamine shock was found to be remarkable, not only in a given species, but when the comparison extended to species in which the prominent group of symptoms varies in its type. In anaphylaxis, the seat of poisoning, as Dale showed, is in the reacting organ; and according to his view it is due to the union of the poison introduced and the special protective substance, or immune body, previously present, and formed there as a consequence of the sensitising dose of poison. Proceeding from this basis there were alternative explanations to offer for the ultimate reaction. Firstly, it could be suggested that histamine introduced affects the reacting cells by producing in these a physical change, of a kind identical with that produced in them when stimulated in anaphylaxis (Dale and Laidlaw). Secondly, it could be supposed that anaphylactic poisoning liberates H-substance and that the visible response is the result of this liberation. In Fig. 28 the two views are represented in their application to skin. Injuries are represented as directly affecting cells (*c*) of the skin. These liberate the H-substance (*H*). Such a substance, liberated or directly introduced from without, has three independent actions; it dilates the minute vessels (action *x*) and increases their permeability (*y*), it acts on a local nerve mechanism and sets up reflexly an arteriolar dilation (*z*). According to the first view (left-hand diagram), the antigen (*a*) when introduced must call forth each part of the triple response, by a direct and appropriate action on the structure (vessels wall or nerve) that is concerned. But

it was difficult to imagine that the three independent actions could be provoked in precisely similar proportions by two entirely distinct agents, antigen and histamine, and we were therefore reluctant to adopt this view. It seemed to us inevitable that we must explain the recurrence of so complex a reaction in seemingly quite distinct circumstances, by seeking one simple underlying determinant ; and so we expressed the second view, that the noxious substance (or antigen) produces its reaction through an identical mechanism to that of injury, namely, by releasing H-substance, which proceeds to act in its accustomed fashion (right-hand diagram). The explanation has the obvious merit of simplicity. Although it has been

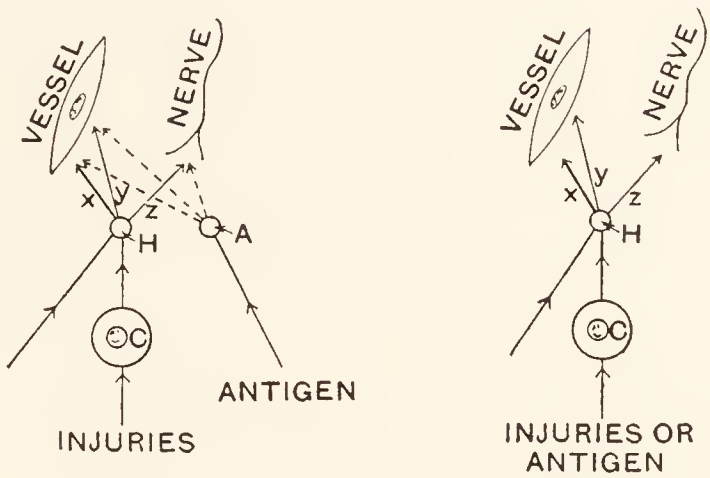


FIG. 28

criticised by Leeuwen and Patot,* there has appeared no substantial reason for changing it, decidedly not so far as it applies to the natural phenomenon of skin sensitivity, though there has been more reserve throughout in regard to the explanation of the artificial phenomenon anaphylaxis. Actually in quite recent times, the work of Feldberg and his associates† has gone far to establish the fact that histamine or a substance closely related to it is to be discovered by biological tests in the blood issuing from the lungs of the guinea-pig in anaphylaxis.

The enquiries upon the sensitised human skin form a first example of the manner in which the original work on triple response expanded and of the use made of a generalisation. They also show again that a relatively simple observation upon a human

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* Leeuwen and Patot, *Zeitschr. f. Immunitatsf., Vol.* LXII, *p.* 410.

† Bartosch, Feldberg and Nagel, *Pflugers Archiv, Vol.* CCXXX, *p.* 129 and 674.

patient may have immediate and important bearings of wide application.

NOTE —The original observations on anaphylatic skin reactions, with references, will be found in the following papers. Lewis and Grant, *Heart, Vol.* XIII, *p.* 219 ; Hare, *Heart, Vol.* XIII, *p.* 227 ; Lewis, "*The Blood Vessels of the Human Skin and their Responses*," *London*, 1927.

## TRIPLE RESPONSE TO COLD.

In speaking of the triple response of the skin to the stimulus cold, it is to be said at once that we are not concerned with the reaction of the skin that has just been frozen. It is true that freezing gives the characteristic triple response, as Love and I showed in 1926 ; and it does so because the cells of the skin are damaged by the crystals of ice forming within them. We had also observed whealing of the skin after it has suffered the remarkable cooling (to —10 or —15°C.), which it withstands for many minutes without actually freezing ; but supercooling does not usually cause a reaction, and the precise circumstances in which it does and the meaning of such whealing still remain obscure. The phenomenon now to be described is quite distinct from this.

Though I had not actually encountered a case, previous clinical records had made me aware that there are rare instances of a curious susceptibility ; the skin of such patients wheals after exposure to cold air or after contact with cold objects, such as metals, although the cooling is not necessarily to freezing point or even near to it. For some years I had in mind the possible importance which hæmoglobinuria resulting from cold might possess for these cases from the standpoint of analogy ; for, while liberation of the contents of the corpuscle acted on by of cold obviously happens in hæmoglobinuria, a similar liberation of the contents of the skin cells, on the basis of our previous conclusions, would account for the whealing of the skin to cold. When in 1928, Dr. Kenneth Harris told me that attending our hospital was a patient in whom bloody urine and nettle rash were *both* apt to follow exposure to cold, the importance of the case, and the exceptional opportunity which it presented, was at once realised. The case became the basis of a report which Dr. Harris and I published with Miss Vaughan, whose aid in studying hæmolysis, of which she had special

experience, we were fortunate to secure. Our studies of this patient will be outlined quite briefly. But first it should be said that although the association of paroxysmal hæmoglobinuria and urticaria from cold as manifestations of one disease was not clearly recognised when our enquiry began, we were able by searching through past records to discover a group of cases, sufficient in number and in clearness to make it certain that this is a recurring clinical type.

Our patient was a healthy-looking girl of 11 years, probably infected congenitally by syphilis. For two years exposure to cold had caused swelling of the skin of the hands and parts of the face, and subsequently the passage of dark red urine. The facts as she related them were confirmed and extended by observation. Half-an-hour after exposure of a large area of skin to cold, red urine was passed, and this was found to contain large quantities of free hæmoglobin. The skin was tested by making contacts with a small metal box through which water of known temperatures could be circulated. The skin reacted normally to histamine and to stroking. It reacted abnormally to cold ranging from 0° to 19°C. and applied for $\frac{1}{2}$ to 5 minutes; the whole skin showed this abnormal susceptibility and so did the mucous membrane of the lip. First of all this reaction of the skin was closely examined and in detail; it proved in every way characteristic of the usual triple response, consisting of local reddening, flare, and wheal, the lesions being indistinguishable from the familiar response to injury, and being accompanied as usual by itching. Skin in which œdema in response to cooling was prevented from developing by circulatory arrest and warmth, was found to be refractory, or relatively so, to the stimulus of renewed cooling and to histamine. Thus we became satisfied that the curious susceptibility to cold just described again exemplifies damage to skin cells, resulting in liberation of H-substance. Our next step was to explain the manner of this supposed release, and here we were guided by our analogy between liberation of the contents of skin cell and the release of hæmoglobin from the corpuscles. For Donath and Landsteiner, and Eason, had demonstrated the presence of a hæmolysin in the blood serum of patients displaying simple hæmoglobinuria after exposure to cold. They also demonstrated by appropriate tests upon the drawn blood of their patients that the phenomenon can be seen and analysed

*in vitro*; thus they were able to conclude that the hæmolysin circulating in the blood unites with the blood corpuscle while this is cooled in its passage through the skin vessels, and that hæmolysis occurs when complement is able to join in the reaction after the blood corpuscle returns to the warmth of deeper lying parts of the body. The blood of our patient was found to behave in exactly the same way, thus displaying the nature of her hæmoglobinuria with certainty. Would our analogy hold? Could we produce evidence of a lysin that would act upon skin cells?

It was found that whealing failed in the skin of this patient as long as cooling (to 10°) was continued, though histamine meanwhile caused wheals to appear on the same skin; though possibly due to a different cause, the natural interpretation of this observation was that cooling of the skin was by itself insufficient, rewarming was essential to the reaction. But conviction came from another source. Our patient was syphilitic, and to avoid the chance of infecting ourselves, we used for our tests cases of aortic disease of proved syphilitic origin. Intradermal injections of 0·1 cc. of our patient's serum were made into the arms of these subjects, and $\frac{1}{2}$ to 2 hours later, when the little swellings of the skin caused by the injections had subsided, this skin was cooled for 5 minutes at 10° and then rewarmed at 35° for 3 minutes. In all instances the skin so treated developed characteristic whealing with surrounding flare at the sites of the injections. Control injections of the serum of a normal subject, tested simultaneously, gave no such reactions. Thus clear evidence was obtained, as our hypothesis had led us to expect, that the blood of the patient contained a substance capable of sensitising the skin of other subjects to cold.

By good fortune a man of 64 years having a similar susceptibility of the skin to cold, but presenting evidence neither of hæmoglobinuria nor of a hæmolysin in the blood, came a little later under observation. A characteristic triple response was obtained by cooling this man's skin to 10° for about 10 minutes. The susceptibility to cold was readily transferred to the skin of our own arms by small intradermal injections of the patient's serum.

These were the main observations, supplemented by others for which the original paper may be consulted, leading to the

conclusion that susceptibility of the skin to cold is due to a "dermolysin" circulating in the blood. To review those observations, which concerned the relation of this substance to the hæmolysin discovered to co-exist in certain of these cases would take us too far afield.

These investigations form a second example of the fruitful expansion of the original work on triple response. Starting again from the generalisation that the triple response invariably means that H-substance is involved, a patient suffering from both hæmoglobinuria and the triple response on exposure to cold presented a unique testing ground of the theory of release of cellular substances. The studies, while bringing most satisfying support to the general theory, unveiled a naturally occurring lysin having its action upon the cells of the skin, and explained a rare susceptibility to cold.

NOTE.—The original observations and references will be found in the article by Harris, Lewis and Vaughan, *Heart, Vol.* XIV, *p.* 305.

## ANNULAR ŒDEMA.

With the help of Dr. Y. Zotterman the following observations were made upon a curious skin eruption occurring in a case of subacute infective endocarditis that came under my care. The lesions appeared on the patient's legs in the form of rounded nodules, raised above the general level of the skin ; these nodules were obviously due to local œdema of the skin and were often a little flushed. The nodule developed (Fig. 29) by spreading slowly at its margins in every direction ; after enlarging a little in this way it became dimpled in its centre ; as it enlarged farther the central dimple gave place to a flat and circular central area, surrounded on all sides by the still advancing rampart of œdema. At this stage the whole lesion would be 3 or 4 cm. in diameter and the rampart about 2 mm. high and 3 or 4 mm. in width. Two lesions developing side by side, and meeting in their spread, would coalesce ; and it was notable that wherever two waves of travelling œdema met both were arrested and all œdema here sudsided.

To explain the development of this curious annular lesion we assumed that the original nodule resulted from a poison released locally in the skin and that this poison spread radially

from a central point, injuring the cells of the skin and releasing H-substance from them in its progress. Thus we accounted for the nodule of œdema, spreading at its margin. The central dimple, enlarging to a circular area bounded by a rampart, was explained by assuming that, as is usual after the H-substance has produced œdema, the vessels that have been affected become impermeable again and refractory to further stimulation. The œdema which formed was short-lived and new œdema could form only where skin previously unaffected became involved. The idea was at once confirmed by testing the central flat areas

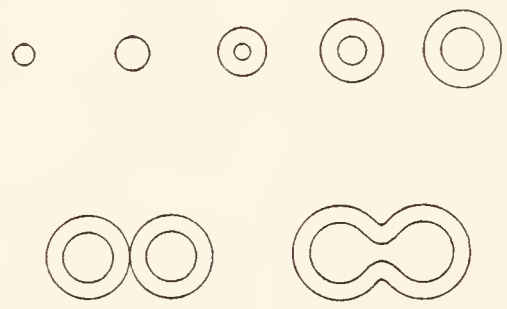


FIG. 29.—A diagram illustrating the gradual development of a single nodule through the phase of dimpled nodule to annular lesion. In the second line two annular lesions in spreading come into contact and then coalesce to form a figure of eight.

with histamine itself; this skin refused to wheal or whealed very slightly.

Many of the developing lesions were closely watched by accurately outlining them during their growth from day to day. Thus on the 7th day of the month a group of 9 lesions, two simple nodules (Fig. 30 *b* and *f*) three dimpled nodules (*a*, *c* and *g*) and the rest annular lesions with flattened centres, were outlined. By the 10th day, these lesions had spread and new ones had developed (*j* to *m*), all becoming confluent with the exception of three (*b*, *c* and *j*). No new *spreading* nodules appeared after the 9th day. By the 15th most of the lesions had run together to form a chief lesion bounded by an irregularly shaped rampart, broken here and there where its œdema had subsided. The rest of the irregular rampart became lost during subsequent days, its gradual and simple subsidence being complicated only by the appearance of small fresh nodules, as at *r*, *s*. It was noteworthy that these final nodules failed to spread and appeared

only at points at which the old rampart of œdema was disappearing or had actually gone. Our theory also explained the final stages of subsidence and the appearance of this last crop of nodules. When lesions developed near to each other and coalesced, progress would be governed by further movements of the poison. In some directions the poison would advance directly into fresh skin, continuing to wheal it until the poison exhausted itself or became too dilute to be effective; so the

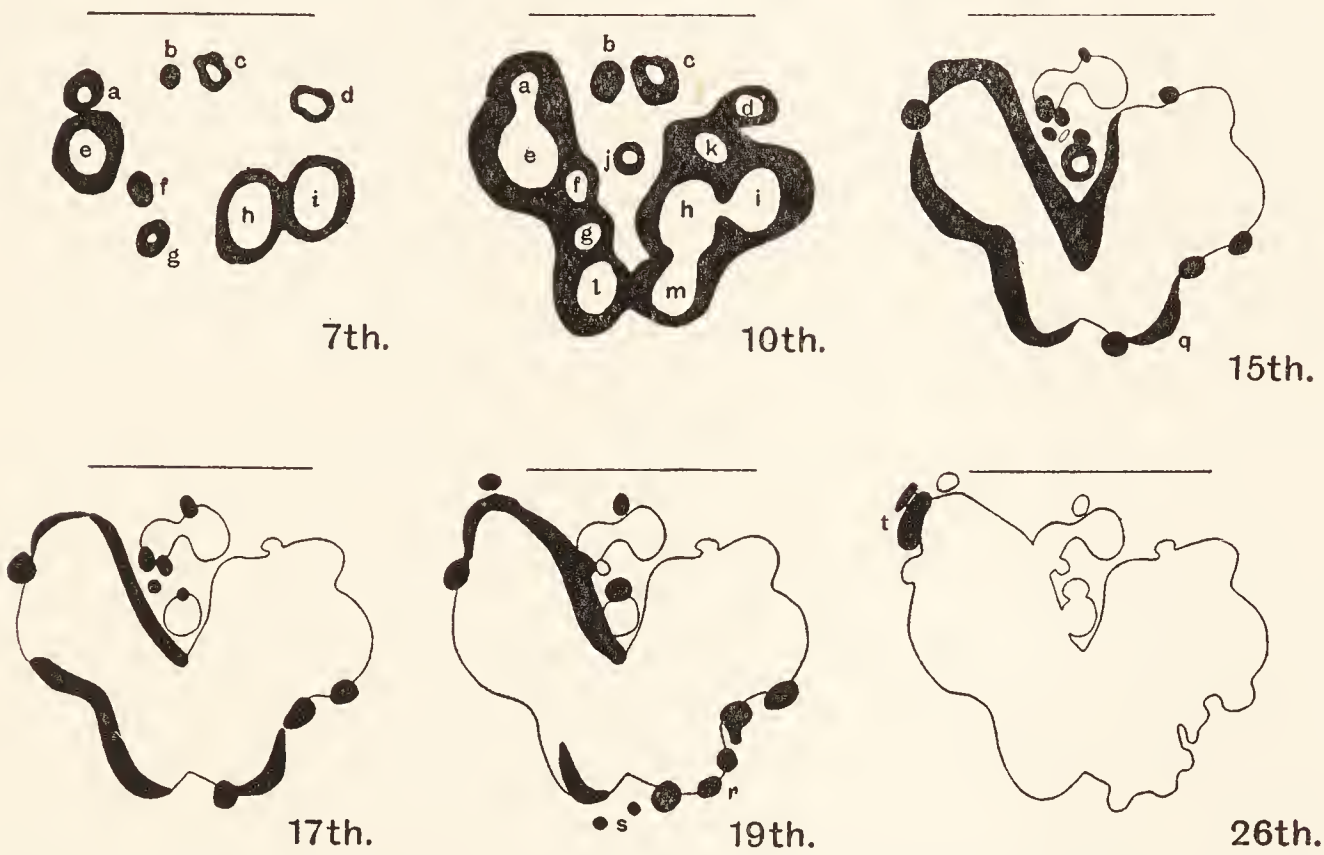



FIG. 30. (About $\frac{1}{4}$ nat. size.) A series of six tracings taken from a group of lesions appearing above the left knee, to show the manner in which these developed, coalesced, and subsided. The day of the month is given with each tracing. The horizontal line represents a fixed mark on the skin. Areas of œdema are represented as black areas; a simple line marks the last points to which previous œdema extended.

advancing wave of œdema would eventually dwindle and disappear. Elsewhere, as when two waves met, the poison would remain in the central area of skin although the fused rampart of œdema subsided, and would continue to move through this area of skin, which, being refractory, could give no sign of its passage; nevertheless, from time to time and from place to place, the poison would cross one of those lines marking the farthest progress of the earlier wave; reaching fresh skin it would act and a fresh but transient nodule of œdema would appear.

Thus an application of the observations upon refractoriness described in the last chapter allowed us to explain with relative simplicity the development of a cutaneous lesion of highly complex and otherwise quite inexplicable form. There are many cutaneous maladies in which curious annular or gyrate configurations occur ; there is no reason to disbelieve that the meaning of the patterns will be resolved by simple and appropriate studies within our powers. To speak more generally there is in my mind no doubt that a large proportion of the innumerable and curious phenomena, which we witness at the bedside, would yield up their meaning to thoughtful and persistent enquiry, and in so doing would advance knowledge not only of the corresponding diseases, but of the relevant processes and reactions of the human body.

NOTE.—The original observations will be found in more detail in Lewis and Zotterman, *Heart, Vol.* XIII, *p.* 193.

## REACTIVE VASODILATATION TO COLD.

One day during the winter of 1927-8 I went out to play in the snow with my children. After re-entering the house I became aware of the burning warmth of my hands. But this sensation, previously experienced many times, on this occasion held my attention ; I began to think of its meaning. An hour later I went out again and held a ball of snow in my left hand for 15 minutes ; then dropping it and going indoors I soon noticed that the left hand was warming, and that in a short time it was quite obviously hotter than the right one. Next day I began deliberate investigations in my laboratory. It was found that the after-reaction to cold could be obtained from a single finger with regularity by exposing it to temperatures of 0° to 7° for 10 minutes. Later it was discovered that the vasodilatation actually begins during the exposure to cold. A thermal junction is fastened by small pieces of adhesive plaster over the end of the finger and the finger is plunged into crushed ice. The temperature of the finger begins to fall at once and continues to fall for several minutes ; then the curve of temperature turns (Fig. 31), rising rather abruptly by as much as 5° or more. This rise, occurring as it does while the finger is still surrounded by ice, must represent an almost full vasodilatation. Enquiry showed

that it can be elicited from the fingers and toes, the palm of the hand, the ears and other parts of the face, and sometimes very slightly but definitely from the skin of the forearm. Temperatures of 0° to 10° produce the reaction easily in the finger, and further tests showed that cooling to 15° or even 18° is a just sufficient stimulus. The reaction can be elicited especially well in those parts of the skin, the temperature of which is especially prone to

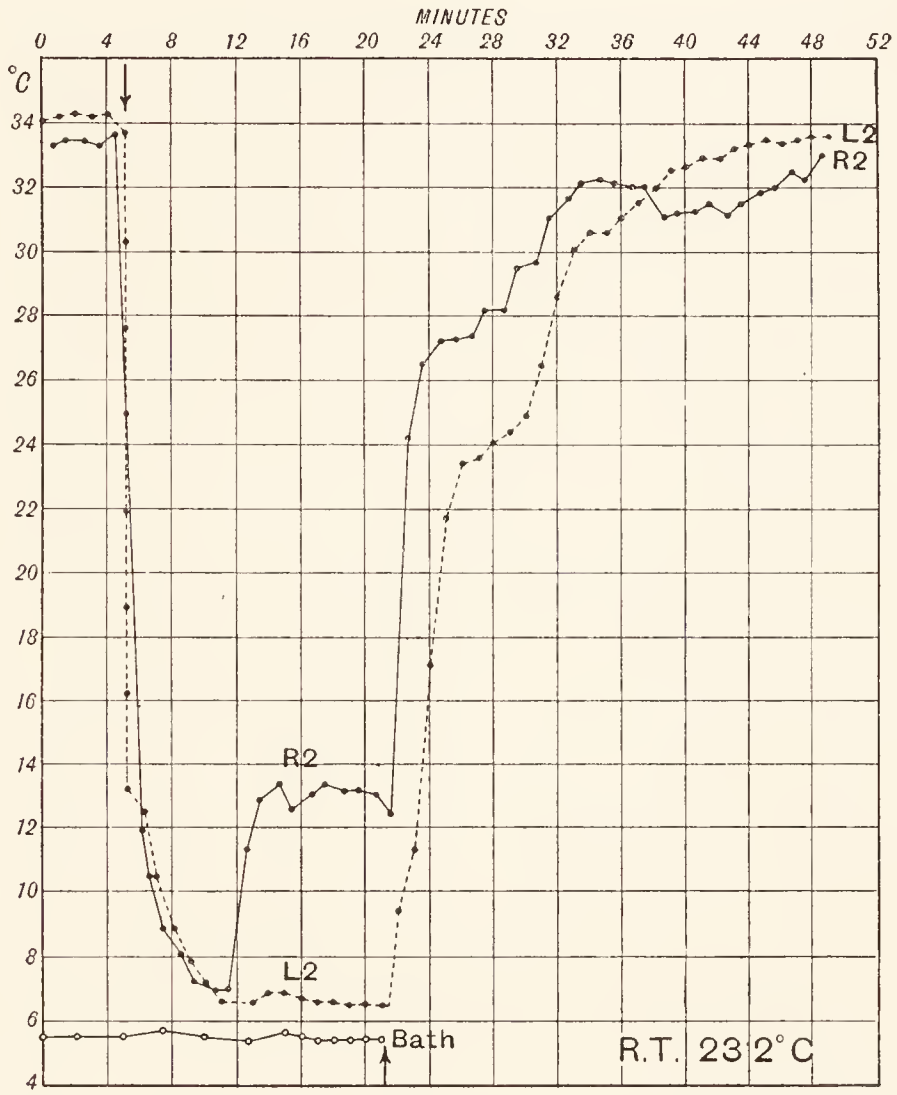



FIG. 31.—Continuous temperature curves showing the effects of immersing the right (R2) and left index (L2) fingers in water at 5·4° for 17 minutes. The instants of immersion and withdrawal are marked by arrows. The left index finger was used as a control, the circulation to this arm being stopped throughout the period of immersion. Room temperature 23·2°.

fall during exposure out of doors. Direct observation actually shows that the reaction is frequent in healthy people while out of doors, when the temperature is between 0° and 10°. It is physiological and manifestly protective. It tends to keep the temperature of exposed skin from reaching points low enough to be seriously injurious; it tends to prevent low points of

temperature being reached, which though less obviously injurious yet benumb and so expose the part to other injuries. It is not confined to man, but occurs in the feet of other mammals such as cats, and is conspicuous, as Grant has since shown, in the feet of birds. The slender toes and legs of small birds, hopping on frosted lawns would freeze almost instantly were it not for this reaction, which is vital to their preservation.

In further investigating its mechanism, the reaction was found to occur in fingers to which all nerve supply has been severed recently, for example, in the 5th finger after accidental transection of the ulnar nerve ; it occurs after the sympathetic nerves to the arm have degenerated following removal of cervical sympathetic ganglia ; but it disappears when, after section of the mixed (ulnar) nerve, sufficient time has passed for the fibres of this nerve to degenerate. Thus it would seem that this reaction in human skin is one depending upon the integrity of the end-apparatus of the sensory nerves, as is the flare of the triple response.

The response was originally attributed to stimulation of the axon reflex by the release of H-substance locally, this release being caused by the action of moderate cold on the skin. Later, some doubt arose as to the validity of this interpretation, although it guided the later observations. It is curious that so intense a response of the arterioles supposedly originating in H-substance release should be accompanied by no obvious local œdema ; other doubts arise from the later work of Grant, Bland, and Camp.* It is possible that in man the sensory nerve end-apparatus is stimulated more directly, yielding a chiefly arteriolar effect, in this instance. The precise mechanism of the reaction discussed remains uncertain.

Out of these observations, and the conclusion that a local vascular response is called into action by moderate cold, arose the further suggestion that under normal conditions an end-apparatus of the sensory nerves may play a definite part in locally controlling the tone of the arterioles and in locally controlling temperature. The conception recognises that a reaction is frequently brought into play by cold, and supposes that there may be frequent reactions to less obvious stimuli. If this conception were correct, degeneration of the sensory nerves should lead to increased tone of the arterioles of the

affected part. In support of this idea is the fact that when fingers are robbed peripherally of their mixed nerve supply, it is the rule for their temperatures to fall and for the fingers to become *persistently* cold and unresponsive ; this is not the case when either the sympathetic or motor nerve supply is lost ; by exclusion the sensory nerves become suspect. It is probable that sensory nerve degeneration, and the consequent disturbance of a local vasodilator mechanism, is largely responsible for coldness and discoloration, which are exhibited by the extremities of patients suffering from peripheral nerve lesions and are amongst the characteristic features of so-called " trophic lesions " in them. The loss of power to react locally exposes the digits to frequent injury by cold, and it interferes with the processes of repair to any form of minor injury by depriving the part, not only of the increased blood supply natural to injury, but even of some part of its ordinary blood supply.

Note.—The original observations are described in the following papers :—Lewis, *Heart, Vol.* XV, *p.* 177 *and* 351 ; Grant and Bland, *ibid, p.* 385 ; Grant, Bland and Camp, *ibid, Vol.* XVI, *p.* 69.

# CHAPTER 9.

## AXON REFLEXES IN MAN.

In this chapter, the meanings of two phenomena encountered in human skin are explained and it is shown how, when the corresponding analysis has been effected, each phenomenon becomes of value in recognising the functional integrity of a particular form of nervous element in the skin. These examples are used to illustrate the investigation and discovery of individual signs of disease, the relation of which to clinical science is discussed more fully in Chapter 15. The nervous mechanism underlying the flare, already referred to briefly in Chapter 7, will be discussed first.

### THE FLARE (SENSORY AXON REFLEX).

The first idea that a reflex may happen in axon branches of a sensory nerve, we owe to observations by Bruce on the conjunctiva (1910). Three years later Müller in investigating the flare appearing around a scratch on human skin, concluded that this is a spinal cord reflex, because he found it abolished in certain instances of gross disease of the spinal column. Breslauer in 1919 investigated the reddening of the human skin that follows an application of mustard oil, and he stated his belief that it results from an axon reflex. The observations of my co-workers and myself on the flares surrounding local injuries of the skin brought us to disagree with Müller's conclusion, relating to the flare around a scratch, and to demonstrate finally that all such flares are derived, as Breslauer had shown for mustard oil, from axon reflexes. Müller was misled by finding the flare abolished in skin segments corresponding to a region of cord invaded by gross disease; he did

not understand that the same disease, by destroying the posterior root ganglia and so causing degeneration of the sensory nerves, would prevent a reflex limited to sensory nerve endings.

Work upon the cutaneous flare has almost been confined to human skin, because this is the only skin known to display it at all conspicuously; and one purpose of discussing the investigations briefly here is to illustrate how collective observation, the use of different types of appropriate patients, sometimes yields an analysis, just as successfully as does a deliberate and varied experimental interference with animals. We found that when a nerve like the ulnar or median, which supplies an area of skin with both sensory and sympathetic fibres, has been divided accidentally, this skin fails to display any flare if the lesion is an oldstanding one. On the other hand, when cases of fresh nerve injury were tested, the flare was easily provoked by any suitable stimulus. Cases that were watched were found to change, the flare being no longer elicited from about the 6th day, namely, from the time at which nerves are known to suffer degeneration; upon such evidence the conclusion could be based firmly that the flare is the result of an axon reflex. To differentiate between a reflex in sensory or in sympathetic fibres, instances of loss of the reflex flare on the facial skin following intracranial operation on the 5th nerve for trigeminal neuralgia on the one hand, and instances in which the reflex was maintained on skin of the arm of patients after they had been treated surgically by excision of cervical sympathetic ganglia on the other, were observed and described. Thus, it was proved that the flare is due to an axon reflex in sensory, and not in sympathetic nerves, nor in a combination of the two.

The proof of a sensory axon reflex in skin not only forms a contribution of clinical science to general physiological knowledge, but it has become the basis of a sound clinical test for degeneration of sensory nerves supplying the skin in man. Thus the test may be used to differentiate between anæsthesia arising from a spinal and from a root ganglion lesion; and it is valuable in determining the boundary between a real anæsthesia and the hysterical anæsthesia, which in longstanding cases of nerve injury often becomes added as an extension.

LOCAL GOOSE-SKIN (SYMPATHETIC AXON REFLEX).

While studying the triple response, as this is provoked by faradic currents, Marvin and I noticed that if currents sufficiently strong to be painful were applied to the skin, an area of goose-skin sprang up around the twin platinum electrodes. Uncertain

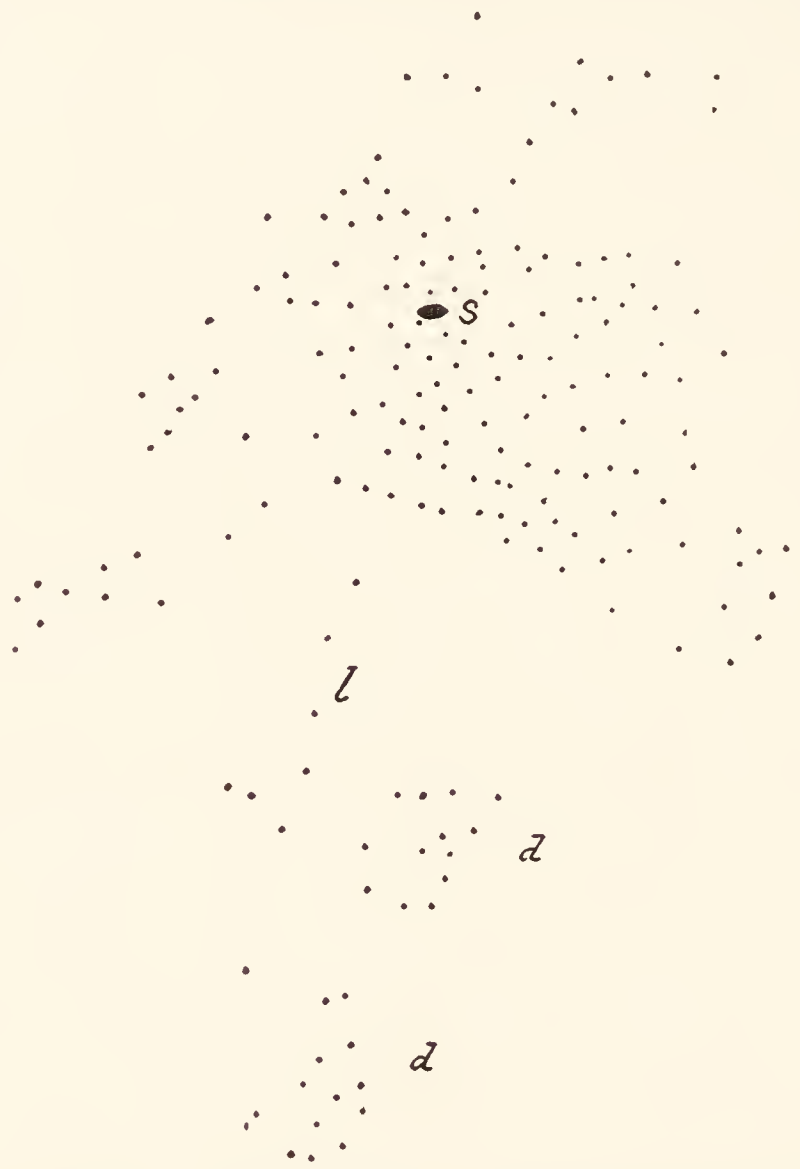



FIG. 32—(2/3, nat. size). The skin of a man's leg was strongly stimulated faradically at a point *s*, the current being continued for a number of minutes. The resultant goose-skin was mapped out by spotting each erected papilla with indian ink. This diagram is a tracing subsequently made from the skin. In addition to a compact area of goose-skin around *s*, it shows outlying projections, a line of six erected hairs at *l* and two islets of goose skin at *d*, *d*. Here and in Fig. 33 the bottom of the diagram represents the distal portion of the reaction on the limb.

as to its explanation, we became interested and decided to investigate. We found that erection of the hairs begins 4 or 5 seconds after the start of faradisation, and that it is full after the current has been maintained for 10 or 20 seconds. On the arm the area of skin presenting this goose-skin may have a

diameter of 5 or 6 centimetres; on the leg it is often larger. When the reaction is full every papilla in the immediate neighbourhood of the electrodes is raised, but nearer the margin some hairs are uninvolved and others are erected a little. The transition from full goose-skin to plain skin is nevertheless relatively abrupt. If the electrodes are moved in any direction from the first point stimulated to a new point a centimetre away, a new band of goose-skin is added on the corresponding side, while a band of about similar extent is lost on the opposite side. Thus the electrodes continue always to lie more or less in the centre of the area of goose-skin, which they provoke. This area of response is never circular; often distinct and even long

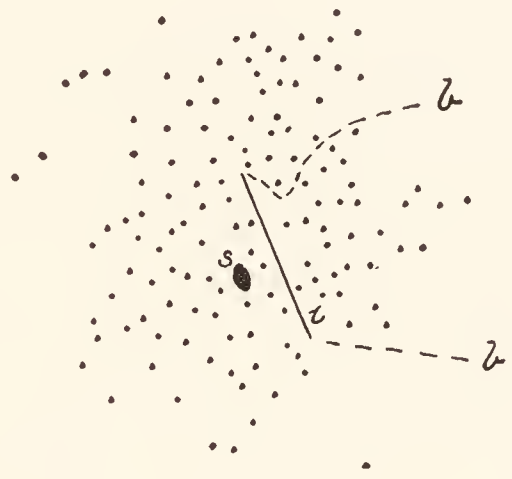



FIG. 33.—(3/4, nat size). An area of goose-skin produced on the upper arm by faradising point *s*. Subsequently, the erection of the hairs between lines *b*, *b* was prevented by an incision *i* just penetrating through the true skin.

promontories jut out from it; and little detached islands of goose-skin may be seen. Some of these radially directed promontories may extend as far as 10 centimetres from the point stimulated. Repeated stimulation of the same point reproduces precisely the same pattern of goose-skin. Now the extent of the reaction and the occasional outlying tongue or island of goose-skin seemed at the time to preclude the possibility of the reaction being due to spread of current to nerve endings or hair-muscles at a distance; but to be sure of this, a fine hypodermic needle was passed into the skin immediately beneath the point of stimulation and 1% novocaine, enough to give a little wheal

5 millimetres across, introduced. This procedure was found promptly and invariably to abolish the reaction, which became attributable therefore to local stimulation of nerves in the skin.

If a cutaneous nerve, carrying as it does sensory and sympathetic fibres to a given area, is cut and time allowed for the fibres to degenerate, then the goose-skin reaction described is no longer obtainable ; the erector muscles can be shown to be capable of functioning, however, for they can be stimulated directly by applying ice to the skin. We found too that simple incisions into our own skins formed complete barriers to the

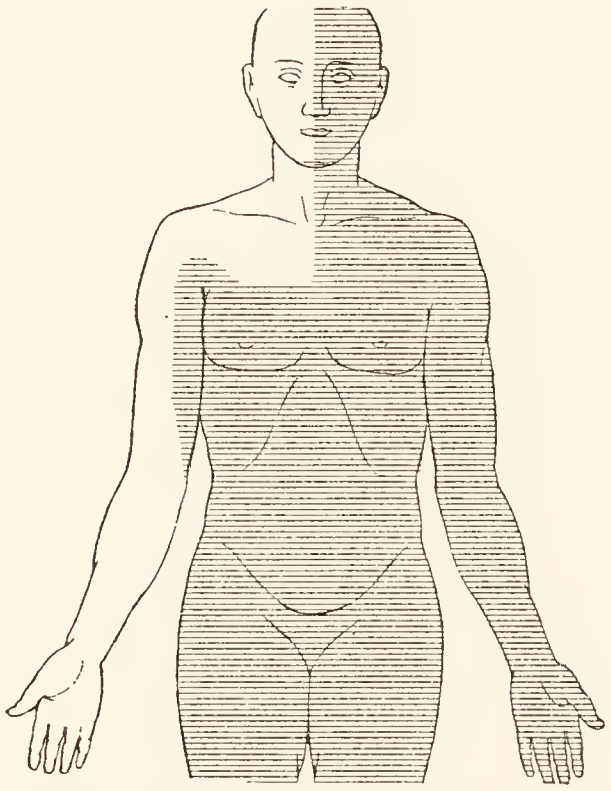


FIG. 34.—The areas of sweating in response to heat displayed by a patient 26 days after excision of the inferior cervical ganglion (*C*.7, *C*. 8, *D*.1) and 2nd dorsal sympathetic ganglion.

spread of goose-skin invoked by faradism, provided that the cut actually penetrated the full thickness of the skin (Fig. 33), but that the cut can be carried almost through the skin without interfering with the response in this way. It seemed probable from these observations that the response happens through axon reflexes in ramifications of the pilomotor sympathetic nerves actually within the thickness of the skin. But such a conclusion would be new to mammalian physiology ; it is true that axon reflexes in preganglionic fibres of the sympathetic had been described by Langley and Anderson ; but here was an apparent instance of a similar reflex in the postganglionic system.

It would have been possible for us, by continuing to mutilate our own skins and by waiting for appropriate cases of nerve injury, to complete the evidence on man himself. But we preferred to make use of the cat, which, so we found, also displays the same local pilomotor response to faradism. It can be obtained without difficulty in pieces of skin that have been excised from cat or man, even if the inner surface of the skin is completely cleaned of subcutaneous tissue. By splitting the cat's skin in the plane of its surface it was found that as much as two-thirds of its deeper layers could be removed and yet an extensive reaction remain.

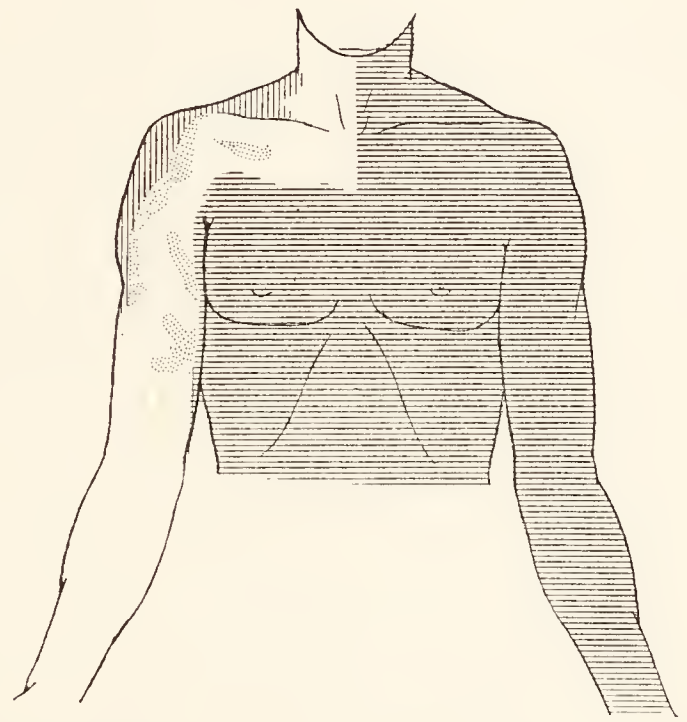


FIG. 35.—The areas of goose-skin obtainable reflexly in the same patient on the 21st day are shaded horizontally ; the vertically shaded areas are those responding fully and the stippled areas partially to faradism.

Histological examination of skin so treated showed that the skin was reduced just to the layer containing the erector muscles of the hairs. If cuts were made penetrating the skin at right angles to its surface, then these began to interfere with the response only when carried two-thirds or three-quarters of the way through the skin. Thus it was shown conclusively that the response is through a system of nerves lying in the skin, but not confined to a particular layer of it. Removal of the sympathetic ganglion, supplying the corresponding area of skin, is naturally without effect on this response ; but when time is allowed for the postganglionic fibres to degenerate after removal of the ganglion, the response is lost.

Thus it was established that an axon reflex is demonstrable in the ramifications of the pilomotor nerves lying actually within the skin. This demonstration, begun upon human skin and for convenience completed upon the cat, not only brought a conclusion of theoretical physiological importance, but gave clinical workers a means of determining, much more accurately than previously, parts of the sympathetic chain involved in destructive lesions, as will now be shown.

The local pilomotor response to faradism arises quite differently to the widespread goose-skin with which everyone is familiar. If the body is unclothed, the mere exposure in a cold room, vigorous rubbing of the back of the neck, and a number of other appropriate stimuli, may result in the spread of goose-skin over large areas of the body. This, as observations upon patients with appropriate nervous lesions have shown, is a spinal cord reflex. The afferent paths are sensory and the efferent paths are sympathetic ; and the latter are broken by cell stations in the ganglia of the sympathetic chain. When a part of the sympathetic chain, for example, the inferior cervical ganglion and 2nd dorsal ganglion of the chain, are excised in man, an excision done in treating "Raynaud's disease" and other affections of the hand, the clinical picture presented is characteristic. The whole of the head and neck and the greater part of the upper limb on that side are deprived of sympathetic supply. The eye is sunken and the pupil small, and the face and hand are usually hotter on that side. The corresponding area fails to sweat when the body is heated (Fig. 34), and over the same area general goose-skin as this has just been described fails. Although goose-skin fails to occur as a spinal cord reflex over the area indicated, it can be obtained within this area as a local response to faradism until, about 8 to 17 days after operation, the nerves involved degenerate ; the response to faradism now fails over those areas of skin the nerves to which have their cell stations in the excised ganglia, but continues to be obtainable over higher segments, the ganglia corresponding to which have been left intact (areas shaded vertically or stippled in Fig. 35).

NOTE.—The original observations and relevant references will be found in the following papers :—Lewis, Harris and Grant, *Heart*, *Vol.* XIV, *p.* 1 ; Lewis, Grant and Marvin, *Heart*, *Vol.* XIV, *p.* 139 ; Lewis and Marvin, *Journ. of Physiol.*, *Vol.* LXIV, *p.* 87 ; Lewis and Landis, *Heart*, *Vol.* XV, *p.* 153.

# CHAPTER 10.

## MUSCULAR PAIN IN INTERMITTENT CLAUDICATION.

### OPENING INVESTIGATIONS.

The term intermittent claudication appeared first in the title of a paper by Bouley in 1831, to describe a condition of lameness in a horse, developing after a short period of exercise and caused by disease obliterating the main artery to the affected limb. The term was soon applied to a similar condition in man, first recorded by Brodie and then by Charcot, and well recognised as a symptom of arterial disease in the limb since Erb established this relation. The chief symptom in the human subject is pain, developing on exercising the limb to which the blood supply is inadequate. Interest in this pain was awakened by a series of patients coming to complain of it; Dr. G. W. Pickering, Dr. P. Rothschild and I determined to investigate it together.

We found that the mechanism of this pain had been a focus of much speculation. Charcot believed it to arise in the muscle of the limb from a form of cramp comparable to postmortem rigor; other writers have expressed similar views, because patients have frequently described their symptoms as "cramp-like pain" or "painful cramps." Although we found evidence that tonic muscular rigidity or true cramp may occur occasionally in certain of these patients, a perusal of past records gave no support to the idea that it is a feature of the attacks. Unwilling to rely upon patients' statements in a matter so important and so easily determinable, on many occasions we closely examined limbs while pain was present in them. These direct observations showed the muscles of the limb to be flaccid during the period of pain, clearly indicating that "cramp" plays no part in its ordinary production. MacWilliam and Webster* also considered

* *Brit. med. Journ.*, 1923, i, *p.* 51.

the muscle chiefly; they remarked that pain arises under conditions involving anoxæmia and its consequences, with excessive accumulation of metabolic products; they did not attribute pain to these metabolities, though the suggestion may be derived from their paper. But the origin of the pain in the muscle itself had failed to win any general support, and more credence had been given to the notion that the pain is arterial in origin and the result of spasm in these vessels (Zak).

In further investigating the pain of intermittent claudication, we took pains to ascertain if pain of an identical kind could be produced in normal subjects by artificially obstructing the circulation to a working limb; for if that could be done with certainty then it would enable much of the experimental work to be carried out under less restricted conditions than upon patients, and by trained observers upon themselves; the use of trained and therefore critical observers has high value where the precise statements of fact relating to a subjective phenomenon are to be obtained. It had long been known that pain soon comes in a healthy limb to which the circulation is arrested by bandage, if the muscles of that limb are worked; but to accept such pain as identical with that described by patients without further evidence would not provide proper security. Satisfactory evidence came in the following way. A patient, having intermittent claudication, the result of advanced obliterative arterial disease of the right leg, and being possessed of a healthy or comparatively healthy left leg, was chosen and the reactions of his two limbs compared. Lying on a couch he was made to flex and extend the right foot fully and rhythmically at the rate of one complete movement a second. At 57 seconds the patient complained of pain over the region of the anterior crural muscles, and at 95 seconds the pain was so severe that he was compelled to stop the exercise. The anterior crural muscles were then tender but quite flaccid. The pain, which lasted $1\frac{1}{2}$ minutes after exercise ceased, was described as precisely that experienced ordinarily in walking. After a suitable interval of rest the leg was retested, after its circulation had been arrested pneumatically above the knee. The result was practically identical with the first test, pain beginning at 63 seconds and becoming intolerable at 93 seconds. The left or healthy leg was now tested. With its circulation undisturbed, this limb could be exercised for long

periods and no pain arose in it ; but if its circulation was first stopped pain began in it at 61 seconds and stopped exercise at 92 seconds. In all the three tests upon the two limbs, in which pain arose, it developed in about a minute, and became intolerable at one and a half minutes. This striking similarity of times is explained by the circulation being either absent or inappreciable in each instance. But the fact is here chiefly relevant because it provided an objective evidence that the pain had the same origin in both the healthy and the unhealthy limb. This evidence was supported by the patient's statement that the pain was of exactly the same quality, distribution, and intensity in his two limbs. It is important to note that this comparison was between the symmetrical limbs of one subject ; for the statement that the pain is the same in both, has in such circumstances exceptionally high value. By studying the pain in the diseased limb of our patient in detail, obtaining descriptions of its character, duration, site, etc., it was possible closely to compare it with pain induced in the limb of a normal subject. In both the pain was found to be a continuous pain, in both it was found to last so long as the circulation to the limb was kept arrested, and to be accompanied by local tenderness ; special testing also showed that it could be brought out at this or that site by throwing the strain particularly on this or that group of muscles ; lastly, the times taken for the pain to begin and to become intolerable were the same in both, provided that the circulation to the muscles was brought to the same state (arrest) in both during exercise. These observations proved beyond all doubt that the pain of intermittent claudication is unconnected with any specific morbid change in those tissues from which it arises, and that in the patients as in the normal subject it is purely a problem of disturbed circulation and its consequences. Having given this evidence, it is unnecessary to detail the corresponding evidence, which is available, to show that pain similarly produced in any group of healthy somatic muscles, is similar in origin, and that this pain of obstructive arterial disease can be studied in any normal limb deprived of its circulation.

The scrupulous identification of the pains in healthy and unhealthy limbs, and its purpose, should be marked ; conclusions presently drawn relative to the nature of pain in a working limb

deprived of its circulation remain unaffected by it ; its purpose is to make these conclusions applicable to the diseased limb ; and that this application may not rest merely upon a reasonable assumption, but so far as is possible upon certainty.

### THEORY OF ARTERIAL SPASM.

The belief that, when a limb is deprived of its circulation and its muscles are worked, pain is caused by the arteries entering a

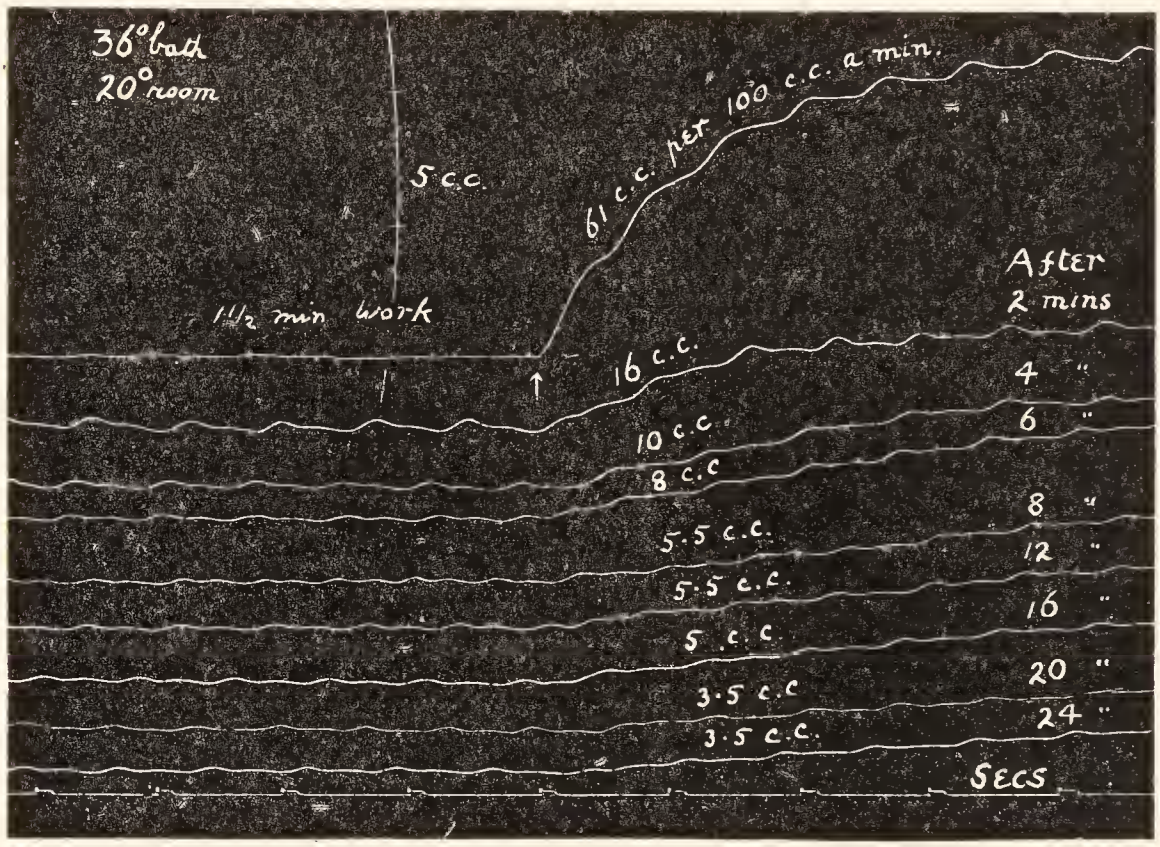



FIG. 36 (reduced).—Successive curves of the rate of bloodflow into the forearm of a normal subject after 1½ min. exercise of the arm muscles with the circulation to them arrested. The brachial artery was released at the arrow, the veins remaining obstructed, and the rate of inflow is measured by the rate at which the arm swells (61 c.c. per 100 c.c. of tissue per minute). The rate of inflow subsequently measured, by throwing an obstructing pressure onto the veins at intervals, shows a gradual decline until in 20 min. it reaches the normal value for rest of 3·5 c.c.

state of spasm, has been supported by no evidence that is not easily and properly interpreted in a different way. On the contrary it can be shown by volumetric measurement of the limb that its vessels are dilated ; for, when the pain is at its height, release of the artery to the limb is at once followed by an unusually rapid entry of blood (Fig. 36).

### PAIN THE PRODUCT OF MUSCULAR CONTRACTION.

When a limb is deprived of circulation and its muscles are worked, pain soon begins in the region of the muscles exercised ; at first slight, it soon grows in intensity. It is a continuous, aching pain ; it does not come and go as the muscle contracts and relaxes ; therefore it is not due to the imposition of tension upon nerve elements. As stated previously, it is not due to cramp, for there is no recognisable increase in the tone of the muscles in which the pain and tenderness are located, neither is there any fixation or uncontrolled movement of the limb. If the circulation is released at the instant exercise ends and when pain is maximal, this pain vanishes completely within 2 to 4 seconds ; but if exercise ends and the circulation remains arrested, the pain persists until the flow of blood to the limb is restored. We were led by this simple but striking observation to conclude that the pain is determined by a chemical (or physico-chemical) stimulus developed in the muscle mass during its exercise. For the stimulus to pain is evidently a stable factor during circulatory arrest, but unstable in the presence of blood supply.

To explore more precisely the behaviour of the pain in varying circumstances, it was first necessary to establish a simple and standard test, yielding a uniform result. The test selected was a grip exerted between the thumb and index finger, recorded isometrically. Almost maximal voluntary contractions are used (developing a tension of 20 to 28 lbs.) ; these contractions are made rhythmically and usually at the rate of one a second. Such movements can be continued painlessly for many minutes if the circulation to the arm is unimpeded ; but if the bloodflow is arrested, pain begins in 25 to 45 seconds and becomes intolerable at a well-defined point between the 60th and 80th second. If each period of preliminary rest is adequate, then in a given individual repeated tests show the time taken to reach the point of intolerance to be surprisingly uniform, variation being usually by no more than 2 or 3 seconds. Having established a test giving such uniform results we were in a position to vary the conditions of the test and so to determine the effect of altered circumstances ; this procedure illustrates the essence of the experimental method.

*Lack of oxygen.* Developing as it does when the muscle contracts under anoxæmic conditions, it is natural to suspect that the pain is the direct or indirect effect of lack of oxygen. But it is not a direct effect, for lack of oxygen by itself is insufficient to produce it. A warm limb to which the circulation is arrested is very cyanotic in 5 minutes ; yet simple arrest for 20 minutes fails to produce the pain. A preliminary arrest of 10 minutes robs the blood in the arm of its oxygen, yet it does not recognisably affect the time taken for pain to become intolerable in the standard test. Perhaps the most conclusive evidence that lack of oxygen plays no appreciable direct part is the following. The usual test exercise is continued until pain begins and the time is noted. After a period of rest the test is repeated and is stopped a few seconds before pain is anticipated. Pain does not develop even though the arterial occlusion is prolonged for another 5 minutes. Now if pain were attributable to lack of oxygen, it is clear that at the instant exercise ends the amount of oxygen in the tissues must have declined almost to the necessary level. Yet, although during the immediately succeeding period oxygen will be used up rapidly, owing to the oxygen debt established, no pain develops.

These experiments placed the direct effects of lack of oxygen out of court; and brought the argument to the point of showing that the process leading to pain is one starting within the muscle fibre and is connected essentially with the contraction process. But they did not exclude the possibility that deficiency of oxygen promotes, or hastens, the process that leads to pain. Actually it has since been shown that lack of oxygen is in this sense responsible, since pain may develop in working muscle that is well supplied by blood, provided this blood is deficient in hæmoglobin (Pickering and Wayne*) or is deficiently ærated (Kissin†).

*Pain related to amount of exercise.* While there is no relation of pain to simple lack of oxygen, it is related to the amount of exercise taken. In the tests, if the rhythm of the muscular contractions is maintained, but the tension developed is increased, the beginning of pain is correspondingly expedited. Secondly, if the tension developed at each contraction is kept constant,

* "*Clinical Science*," *Vol.* 1.

† *J. Clin. Invest.*, *Vol.* XIII, *p.* 37.

but the rate of contraction is doubled, then the period of work necessary to produce pain is approximately halved ; in other words, the same number of contractions is required to produce pain whether these occur in quick or slow succession.

"*Factor P.*" The conclusion reached from the experiments described, and from supporting evidence presently to be given, was that when muscular exercise is taken in the absence of blood supply it leads to pain, and that the responsible stimulus arises out of the contraction process. For reasons that will be given later the stimulus causing pain was assumed to act on sensory nerve endings in the spaces between the contractile fibres. When muscle contracts, changes, such as a formation of metabolites, occur within its fibres. One obvious possibility is that such metabolites diffuse out and comprise the agent stimulating the sensory nerve endings ; but it seemed desirable to avoid drawing a conclusion in this definite form, since it is also possible that changes within the fibre may induce secondary but distinct changes in the spaces. It was necessary to keep the relevant changes within and without the fibre as separate ideas ; this was done by naming the latter "factor P," because it is the immediate stimulus to pain.

*Recovery.* In the standard test on the normal arm, the time taken for pain to develop from its beginning to its intolerable point is about 35 seconds. The amount of "factor P" responsible for this development of pain is dispersed within about 3 seconds of restoring the flow of oxygenated blood to the muscle. "Factor P" might be regarded as comprised in a process rapidly reversible in the presence of fresh blood, or as being in fact a chemical substance that passes easily through the vessel wall to be dispersed by the circulating blood. Recent observations emphasise the importance of a return of oxygenated blood to the muscle as necessary for quick relief of pain.

The prompt relief of pain on releasing the circulation is not to be interpreted as meaning that there is complete recovery of the underlying process within the muscle fibre, but only that the accumulation of "factor P" outside the fibre has been reduced below the pain level. If the standard test is repeated without an adequate rest period intervening, although this period may be more than enough to abolish all pain, then in the second

test pain appears more rapidly than in the first, and it appears all the more rapidly, the shorter the rest period.

*Muscular exercise with free circulation.* When the muscular exersise of the ordinary test is undertaken with the circulation free, there may be a little ache in the arm, but pain clearly identifiable with that here studied does not arise. From this it is not necessarily to be concluded that "factor P" fails to develop in these circumstances, since conceivably it rises with the contractions and falls in the intervals, and thus fails to reach the pain producing level. From this standpoint it is important to ascertain the influence of a preliminary muscular exercise, with free circulation, upon the subsequent development of pain with circulation arrested; it is found that the time taken for pain to develop is reduced, showing that the process fundamental to the production of pain is natural to the muscle while fully supplied with ærated blood. The longer the period of the preliminary exercise the shorter is the time required for pain to develop in the standard test; during the preliminary exercise there is a process of accumulation.

*Latent pain.* The experiments now to be described were those which led us to conclude, as foreshadowed, that the pain factor acts, not in the muscle fibre, but in the tissue space. It has just been shown that during muscular exercise with circulation free, a process of accumulation relating to the development of pain occurs; this accumulation may be regarded as happening within the muscle fibre itself. If the exercise is done and the circulation is then stopped, at the instant exercise ends there is no pain, but pain develops distinctly after a latent period of 20 or 30 seconds and may become severe within a minute. This latency is not to be attributed to a natural delay in the development of "factor P"; for no such delay is suggested by other relevant observations. Thus, when similar exercise is carried out during circulatory arrest and pain comes, it does not increase if exercise is stopped; and, if exercise is carried to a point just short of producing pain, pain does not appear subsequently. The observations decidedly suggest that, while exercise is proceeding, "factor P" accumulates during circulatory arrest to given levels, and that these levels, whether pain producing or not, are maintained if exercise ends and the circulatory arrest continues. But if the blood is flowing during exercise, then,

although the chemical changes in the fibre will be cumulative, "factor P" will not necessarily accumulate correspondingly in the tissue spaces, or to a level sufficient to stimulate the nerve endings. According to this view the latent period from occlusion to the appearance of pain is a period during which "factor P" is rising in the tissue spaces to a level corresponding to the state of the fibre. Thus the fuller hypothesis takes the form that a product of muscular contraction is directly or indirectly responsible for pain; that, when successive muscular contractions occur in the absence of bloodflow, the state of the muscle alters progressively and that *pari passu* "factor P" accumulates in the tissue spaces; but that when the muscular contraction occurs in the presence of bloodflow, although the same change happens in the muscle fibre, "factor P" cannot rise to the corresponding level in the tissue space. Clear support for this idea is obtained from a related observation. The exercise is undertaken with circulation arrested for a fixed period, which is sufficient to produce considerable pain. The circulation is now released for a chosen period of time and re-arrested, and the time at which pain reappears and the intensity it reaches are noted. The period of release is suitably varied in distinct observations. It is found that the period of latency is less according as the period of release is less; and that the intensity reached by the pain, and subsequently maintained, is greater the shorter the period of release. This is readily explained on the ground that the state within the muscle fibre at the instant the bloodflow is re-arrested will vary with the previous duration of that bloodflow. After a short release recovery in the muscle will be slight and on re-arrest "factor P" will rise quickly to the pain producing level, and subsequently to a high level in the tissue space, and pain will be considerable; after a long release recovery will be greater and, on re-arrest, "factor P" will rise more slowly to the pain producing level, and ultimately to a lesser height, and pain will be slight.

As previously indicated, the quick disappearance of pain on release of the circulation in the standard test is to be interpreted as due to the prompt reduction of the level of "factor P" in the tissue spaces, and not to recovery of the muscle mass as a whole. The ordinary failure of pain to appear in muscular exercise with intact circulation may be attributed to adequate interchange

between tissue space and vessel in which oxygenated blood is flowing rapidly.

## COMMENT.

The observations and experiments of this chapter serve to illustrate a simple form of the experimental method in clinical science. A manifestation originally observed in a patient is deliberately and repeatedly provoked under constant conditions, so as to obtain in the first instance a uniform result; the conditions are then varied and the effects of these variations become the object of reasoned study. They illustrate the appropriate selection of control observations; the first comparison of a phenomenon in symmetrical limbs of one subject, in preference to a comparison between the diseased limb of one subject and the healthy limb of another. They illustrate how the scope of investigation may be enlarged and the description of subjective phenomena rendered more precise by provoking the symptom artificially in normal men and trained observers; safely and profitably enlarged if it is ensured that the manifestation provoked is really equivalent to that induced by disease and originally under study.

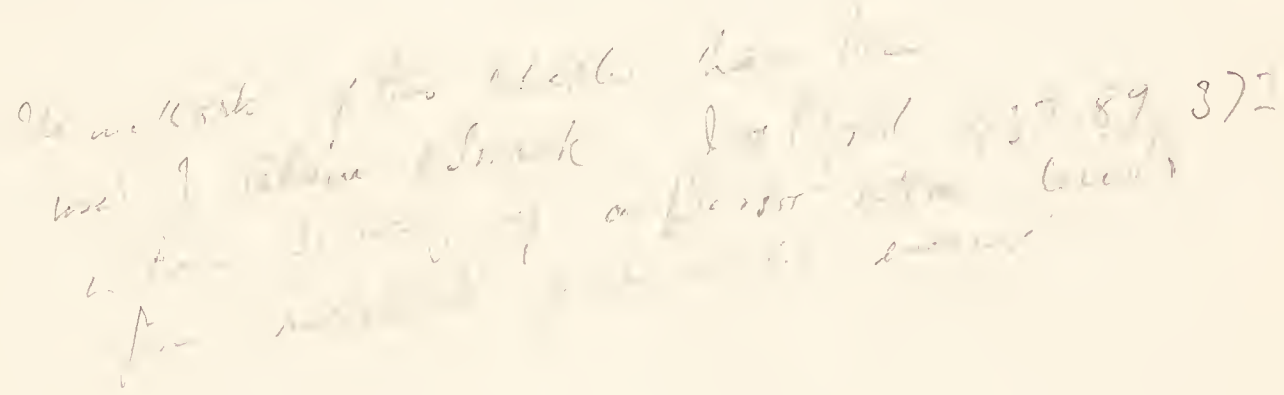
The results of these investigations had their most direct and practical bearing upon the condition called "intermittent claudication" in patients, providing a clearer understanding of this state, of the manner in which its pain originates, and of its behaviour in different circumstances of everyday life; thus throwing light upon the disease and helping us to a rational interpretation of its several manifestations. When the circulation to a normal leg is stopped, and the limb is exercised, pain soon begins and waxes to an intolerable point. The pain resulting when a limb, which is the subject of arterial disease, is exercised, may come as quickly or it may arrive more slowly; obviously we can form a reasonable estimate from this time relation of the extent to which the arterial conduits have suffered. We can form a similar estimate from the time taken for the pain induced by exercise to pass away; for with the return of bloodflow through normal vessels the pain vanishes within a few seconds, whereas with the return through diseased vessels, the recovery may be a matter of minutes or of an intermediate period of time. In these and in many other directions the

information obtained by study is helpful in the management of the corresponding patients.

The proof that pain can arise from a natural chemical or physico-chemical stimulus, by the investigations here described, led to the enquiries into the burning pain of skin injuries to be recorded in Chapter 14 ; they were the immediate stimulus and guide to the observations and conclusions on angina recorded in the next chapter, in which further comments on investigational method will be found.

Lastly, these investigations illustrate the almost invariable trend of enquiry into the meaning of symptoms displayed by patients. Since symptoms are due to disturbed function, their investigation transports us at once to, or beyond, the boundary between medicine and physiology. This form of contact with physiology affords the chief opportunity of applying current physiological teaching to problems of disease. Simultaneously the contact presents to the purely physiological student new aspects of questions already familiar to him, and new and profitable lines of work. Contact between these investigations of pain arising from working muscle in man and physiological studies of sensory nerve impulses arising from muscle in the cat has already been established in recent physiological studies,* and will no doubt lead to the mutual inspiration of both branches of work.

Note.—The original observations of this chapter are fully described in Lewis, Pickering and Rothschild's paper, *Heart, Vol.* XV, *p.* 359.



* Matthews, *Journ. of Physiol., Vol.* LXXVIII, *p.* 1.

# CHAPTER 11.

## ANGINAL PAIN.

### ANGINAL PAIN AND THE THEORY OF MUSCULAR ISCHÆMIA.

The idea that angina pectoris can arise out of a morbid change in the coronary vessels came from Edward Jenner ; but it was Parry who in the year 1799 first clearly enunciated the idea that the symptoms result from what has come to be called *relative ischæmia* of the cardiac muscle. Parry believed that diseased coronary vessels, though capable of conveying an adequate quantity of blood to the heart when it beats quietly, may be unable to convey enough to supply its wants in vigorous action. His idea, though frequently discussed and even linked in the discussions with the origin of pain of intermittent claudication, was unable to take any firm root, owing to its depending upon a slender and indirect evidential basis. Innumerable hypotheses meanwhile sprang up to explain the origin of anginal pain, including that which supposed that the anginal attack is provoked by a sensitive aorta being thrown into a state of unusual tension ; but none of these until quite recently has come near to general acceptance. Even the similarity between the pain of coronary occlusion and that of recurrent anginal pain failed to carry conviction, since pain in the former could be explained as derived directly from the vessel wall or from the pericardium, rather than from muscle deprived of its blood supply. The full significance of comparing pain arising in a working limb and in the heart, each inadequately supplied by blood was not grasped, and the comparison did not lead beyond a simple analogy and to a firm conception of a fundamental pain factor common to the two instances until the mechanism of the pain was analysed closely, and information obtained as to its behaviour in well defined circumstances. This work, carried

out on somatic muscle, has been described in outline in the last chapter ; for the first time it has brought us a secure basis for thought. It has led to the conclusion that pain arising from somatic muscle, deprived of its blood supply, is due to a pain factor (almost certainly chemical in nature) arising out of the contraction process and accumulating in the muscle mass. It is highly important to note how this definiteness of conclusion has resulted in progress ; so long as it was merely thought hypothetically that pain might be due to muscular ischæmia, so long were there strong rival hypotheses, such as that which supposed spasm of the arteries to be concerned, and so long did a sense of insecurity call halt to further consideration. A proper evidential basis alone gave confidence for the next steps. It is of historic interest to remark in this connection that just as a pain in an ischæmic working limb was at one time thought to result from cramp of the muscle, so the notion of a cramp in cardiac muscle has been used, among innumerable other and plausible explanations, to explain angina pectoris. To apply our conclusion as to the cause of pain in somatic muscle directly to the problem of its causation in visceral muscle without further consideration might be legitimate hypothesis ; but it would involve the small assumption that the products of somatic and visceral muscle are similar to the extent that in both the same "factor P" is produced ; it would involve the larger assumption that, accumulating in cardiac muscle, this factor would stimulate sensory nerve endings and cause pain. Such assumptions became of diminishing consequence, and the hypothesis steadily acquired more of the stability of conclusion, as the behaviour of pain in the two circumstances was found to be similar, and to be explicable upon a common and simple theoretical basis.

If the application of the theory of muscular pain to angina were sound it should at once explain much or all that was previously obscure, and it should lead to predictions, which observation or experiment could proceed to verify. All this happened.

When the arteries of a limb are diseased, a certain amount of work must be done before pain comes ; in cases of early disease this is considerable and work may be done at slow rates without pain arising ; in cases of advanced disease the amount required is less ; in the most advanced cases the blood supply is so small

that the amount of work required to produce pain is practically the same as it is when the blood supply is completely obstructed. Two factors are concerned in the production of pain, namely, the rate of energy expenditure on the one hand, and the quantity of fresh blood passing to the muscle on the other. It is a lack of balance between these two, and the consequent accumulation of "factor P," which ultimately causes pain to occur; and lack of balance is embodied in the term relative ischæmia. It is also known that pain that has once come will not disappear so long as the blood supply is suppressed, but that with full blood supply it will disappear quickly, and with poorer blood supply in time.

We turn to the comparable events in the heart. It has been established beyond any reasonable doubt by clinical observation that pain is produced by occlusion of coronary vessels, and that this pain is indistinguishable from that of spasmodic angina pectoris in situation, radiation, and character. It differs from the spasmodic pain in only one chief particular, namely, in its continuing while the patient rests for long periods of time, for hours, or even days. According to our theory it *must* be long lasting, for the blood supply to the affected muscle has been suppressed and can only be restored, and then rarely effectively, through small collateral channels. When the obstruction happens, the muscle is already working; it continues to work and "factor P" accumulates to the extent of giving intolerable pain, until the muscle is dying; there is no possibility of work being brought voluntarily to an end at any time, as there is in the case of the limb, and even when the piece of heart muscle concerned ceases to work, the pain will continue as long as the sensory nerves in the heart are alive and stimulated. Variations in the intensity of the pain, and in its duration, are to be expected according to the amount of muscle involved and according to the rate at which its nerves die or are relieved by the ultimate dispersal of the stimulus; there is ample scope for simple explanations of such differences in pain as are found, and a clear reason for its usual long duration.

In considering angina of effort on the other hand, it is easy to understand why the onset of pain is so closely related to the heart's expenditure of energy, whether this comes from increased blood pressure or from increased heart rate; and why

rest from the work that induces the attack brings speedy relief ; for work upsets and rest restores the balance. Amyl nitrite, in cases of spasmodic angina, may also restore a broken balance, but its action, according to numerous contemporary observations, is not so much the result of its lowering blood pressure as the result of its dilating the coronary vessels of the affected area ; amyl nitrite does not relieve the pain of coronary thrombosis, for it cannot open the thrombosed vessel and thus reduce the accumulated pain factor.

The presence of a stable underlying stimulus in the ischæmic working limb is responsible for the smooth continuity of the pain ; the pain does not wax and wane with the movements of the muscle. We can now understand why similarly anginal pain is smooth in the same sense, and has no rhythmic fluctuation with the beats of the heart, a question previously puzzling and unanswered.

We can understand how coronary thrombosis, by impairing the nutrition of an area of muscle previously well supplied with blood, can leave the patient subsequently a sufferer from angina of effort ; we can understand how, paradoxically, coronary thrombosis may abolish the angina of effort, if an area of muscle inadequately nourished, is killed by complete suppression of its blood supply.

That deficient æration of the systemic blood, caused by anæmia, or produced by breathing air poor in oxygen, provokes pain from the working somatic muscle and also from the heart in suitable subjects, is another firm link recently established ; in the case of both forms of deficiency an observation relating to one kind of muscle predicted and led to a corresponding observation in the other.*

The idea that compared the pain arising from somatic muscle with that arising from heart muscle is no longer in the stage of simple analogy ; the evidence pointing to their origin from processes fundamentally similar becomes increasingly evident the more closely their behaviour is studied. The comparison between intermittent claudication and angina of effort is particularly striking, for in neither instance is the blood supply to the muscle suppressed, but in both it is presumably inadequate to the needs

* Pickering and Wayne, *Clinical Science, Vol.* 1 ; Kissin, *J. Clin. Invest., Vol.* XIII, *p.* 37. Rothschild and Kissin, *Amer. Heart Journ., Vol.* VIII, *p.* 729.

of the working tissue. It was the work on intermittent claudication which suggested comparable studies upon angina of effort, now to be outlined and recently carried out in my laboratory by Drs. Wayne and Laplace.

### EXPERIMENTS UPON ANGINA OF EFFORT.

It should be stated as a preliminary that in inducing a patient to provoke an attack of anginal pain, we ask him to do no more, while under our close control, than he is in the habit of doing several or many times a day without supervision, when he walks until pain comes ; such tests, undertaken with scrupulous care, are justified by the information they give us about our patients individually.

As described in the case of somatic muscle pain, it was first necessary to ascertain that a patient could be placed under given conditions for work, which in repeated tests would yield uniform results. Little difficulty was expected and little experienced in arranging such tests ; for, as in the case of intermittent claudication so in the case of angina of effort, a patient may relate how pain may arrest his progress regularly as a certain house, or other object by the wayside, is reached in the daily walk. A walk up and down two steps, at a fixed rate, in a warm room, under constant conditions of previous rest and feeding, formed the test, the walk being continued up and down the steps until pain appeared, and the amount of work done being recorded as the number of times the steps were climbed. As soon as pain came, the patient sat at rest, while observations on pulse and blood pressure proceeded, and the duration of pain was noted. In suitable patients the results were sufficiently constant ; thus in four consecutive tests on one case pain appeared after 48, 58, 48 and 50 climbs, and the pain lasted in these tests 97, 90, 90 and 95 seconds respectively ; such patients were used in further investigations. As in the case of the somatic muscle, repetition of the exercise without the intervention of an adequate rest period led to the earlier appearance of pain ; the correspondence is here a close one, for in both instances it is unnecessary for the first test to be carried far enough actually to induce pain, it still has the effect of expediting the occurrence of pain in the second test.

Comparative tests contradicted the old idea that cold directly predisposes to anginal attacks; when measured exercise is taken in hot and cold atmospheres the pain comes after equal amounts of work. Pain is oftener induced in cold weather, because unwittingly anginal patients walk faster at such times.

Comparative tests have confirmed the idea that meals predispose to the attacks, and special tests have demonstrated that mere distention of the stomach is not the factor involved, but that change in the distribution of blood to the viscera is probably responsible.

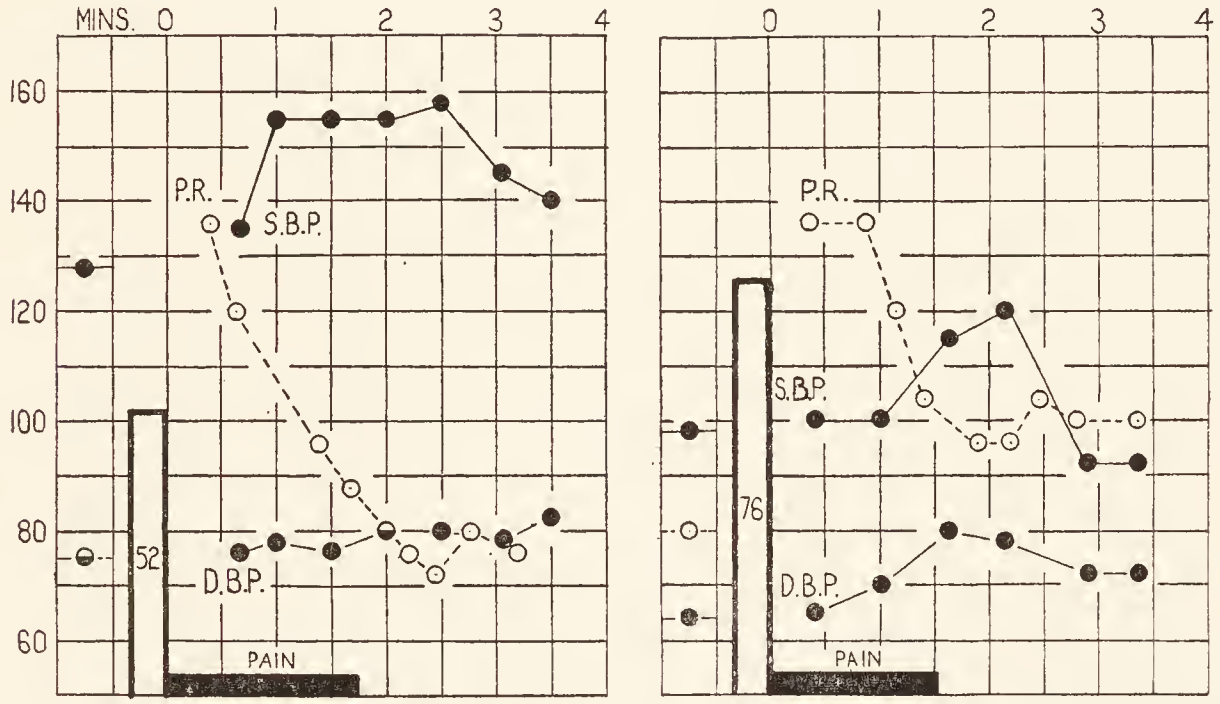



FIG. 37.—(After Wayne and Laplace). S.B.P. = systolic, and D.B.P. = diastolic, blood pressure in mm. of mercury. P. R. = pulse rate in beats per minute. On the left of the vertical rectangle are the resting readings before exercise was begun; on the right are the readings after the patient sat down. The number included in the vertical rectangle and its height represent the number of efforts. The length of the black horizontal rectangle gives the duration of the anginal pain provoked by exercise.

The chart on the left shows a control test, and that on the right the effect of 1·3 mg. (1/50 grain) nitroglycerine given by mouth two minutes before exercise started. The number of efforts necessary to induce pain is increased, and the duration of the pain diminished; pain appears in this test although the blood pressure does not rise above its ordinary resting level, indicated in the chart of the control test.

The method was also employed to test the effect, and to explore the action, of various drugs upon the attack of pain. Thus, the amount of work required to induce pain before and 2 minutes after the administration of a single dose (1/50 grain)

of nitroglycerine was accurately studied, and these studies are exemplified by Fig. 37. To induce pain required 52 journeys over the steps before, but it required 76 journeys after, giving the drug, an exact expression of the increased capacity of the heart to work painlessly. In similar tests the action of other drugs was investigated with precision. In Fig. 37 it is to be noticed that although pain came on exercise before and after nitroglycerine, its presence was independent of a critical level of blood pressure, for blood pressure was actually below normal levels during the period of pain under nitroglycerine, and blood pressure was rising at the time pain passed away. The example is one of many instances recorded in this and related researches indicating that the nitrites do not act as was formerly thought

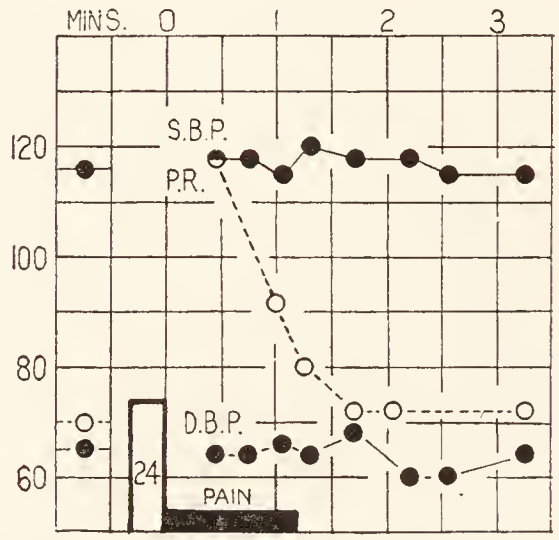



FIG. 38.—(After Wayne and Laplace). An attack of angina provoked by exercise; during the attack the pulse rate, but not the blood pressure, was raised.

by lowering blood pressure, but that their effect is mainly produced through dilatation of the coronary vessels. In the same figure the relation of pain to pulse rate is also displayed, and this relation is one of considerable constancy. Rise of pulse rate appears to be much more provocative of anginal pain during effort than is raised pressure; instances are observed in which pain comes with simple exercise without rise of pressure, but the pulse rate is always raised (Fig. 38). Interesting as these results are when considered individually, they have a wider significance when regarded collectively. They are definitely inconsistent with any view of the origin of anginal pain that refers this pain to an effect of increased tension in aorta or heart; they are

completely consistent, however, with the views that anginal pain can be provoked by increased energy expenditure, such as is occasioned by rise of pulse rate, and that it can be relieved by widening of the coronary vessels. They therefcre bring strong support to the theory already discussed, that anginal pain is the result of relative ischæmia of the heart muscle.

## COMMENT.

Although angina pectoris was described nearly 150 years ago and its relation to effort has been recognised for a similar period of time, only during the last few years has any serious attempt been made to determine the relation of anginal pain to such simple changes in the cardiovascular system as those in pulse rate and in blood pressure. The fact is the more remarkable since for very many years the manner in which anginal pain is provoked has been discussed almost constantly, especially in relation to the strains imposed by effort. The facts have been at the disposal of any who chose to study the cases, and the method of study has been for many years within the easy reach of any clinician. It is very difficult to understand how speculation could have been allowed to replace observation and experiment to the extent it has ; but it may have been due to incomplete appreciation of the danger of accepting as facts things that merely seem highly probable. Because exercise lifts blood pressure in health, that does not justify us in proceeding from an assumption that the same event always happens when exercise provokes anginal pain ; *a priori* there is no assurance that the anginal subject and the healthy subject will react alike. It would be unsafe to assume that nitrites necessarily lower blood pressure in anginal attacks merely because pharmacology teaches that they lower pressure in normal animals. Direct observation upon patients avoids the errors that inevitably follow when working in this way by inference, and reveals facts previously unsuspected. It is requisite for clinical science to work whenever possible from precisely relevant observations. It was at one time widely taught that digitalis is harmful in cases of aortic regurgitation, for the drug had been found to raise blood pressure and to lengthen diastole in animals ; so it was considered that it would increase the amount of blood regurgitating in diastole

in aortic disease. Direct investigation has shown that given in ordinary doses to these patients it has no measurable influence upon blood pressure or upon heart rate; and that in fact it can be given to them from time to time with conspicuous benefit.

In the opening chapter of this book the value of the direct investigation of symptoms, and of provoking and studying these manifestations of disease under controlled conditions, was emphasised. The method has been touched upon in other places in this book, but intermittent claudication and angina of effort have been chosen as chief illustrations.

The investigations on angina pectoris have been described in sequence to those upon pain and intermittent claudication, to illustrate how profitable it may be to widen the scope of investigation when opportunity offers. The first series of observations and conclusions largely prompted the second, suggesting analogous enquiries and interpretations. An investigation upon a somatic muscle, the movement of which and the circulation to which are controllable, thus becomes in a fashion the basis of enquiry into the behaviour of a deeply-seated organ. It is to be understood, however, that reasoning from simple analogy to conclusion must be restrained, and that in relation to the events in the deeply-seated organ, the method is chiefly useful in suggesting explanations, the validity of which can then be tested directly.

NOTE.—Reference to relevant papers will be found in Lewis, *Heart, Vol.* XV, *p.* 305; Lewis, *Arch. intern. Med., Vol.* XLIX, *p.* 713; Wayne and Graybiel, *Clinical Science, Vol.* 1, and in Wayne and Laplace, *Clinical Science, Vol.* 1, *p.* 103.

# CHAPTER 12.

## SUBACUTE BACTERIAL ENDOCARDITIS.

### THE PROBLEM OUTLINED.

It had long been the habit of my laboratory to examine closely all specimens coming from autopsies upon cases of heart disease dying at University College Hospital; and, among these, cases of subacute bacterial endocarditis were scrutinised with particular care, because we had long been interested in this malady, and especially in the very slow but seemingly inexorable march upon which it conducts the sufferer to his death. We were familiar with the well-known lesions characterising this malady; with the almost invariable affection of the left side of the heart only; with the usual spread of the vegetations over two or three cusps of one valve, or over both valves, or over septum; and, of chief importance from our present point of view, with the evidences of healing. To the latter special attention had been paid, and we agreed with previous workers that these evidences are abundant and frequent. Microscopic examination of the granular or pedunculated vegetations showed them often to be in an advanced state of organisation; in elongated vegetations the signs of repair were found to be of older and older type when traced towards the attachment; fresh thrombus was found at the tip, and at the base fibrous elements predominated. When Grant and I discussed these cases together, it was realised that such appearances were to be expected in a malady often lasting six months and sometimes longer, and presenting clinical evidence of infection throughout. Patients dying at any period of this malady always showed relatively fresh vegetations; when we asked what had become of the early vegetations in cases that had been for six months under our care, we seemed to find the answer in the firm scar

tissue at the bases of some vegetations and in the simple scar tissue in other parts of the thickened cusps. But in looking at the lesions from this standpoint, and in attempting to correlate the amount of scarring with the length of the infection, a difficulty arose. This consisted in failure to differentiate sharply between fibrous tissue that might be attributed to healed ulcers and vegetations, and similar tissue that might be regarded as resulting from previous disease of the valves. At the time, the conclusion was widely held that the subacute form of endocarditis may become implanted upon chronic rheumatic valvulitis, because cases remaining years under treatment for simple mitral stenosis or aortic disease were known to develop it, and because typical vegetations might be found upon a mitral valve showing the characteristic deformity of stenosis. It was also generally recognised that cases of congenital malformation of the heart become infected and succumb to the disease. But although cases of these kinds were encountered not infrequently, in the majority of cases coming to autopsy a history of earlier valvular disease could neither be obtained from the clinical history, nor read with certainty from the heart after death. Consequently, although there were cases plainly showing that infection can follow upon old standing heart disease, in the majority of individual cases no reasonably certain conclusion of this kind could be formed ; and so, the frequence of such a sequence of events could not be estimated even approximately. To establish this frequence became our problem ; when it was being closely considered, we had begun to take notice of certain special deformities of the aortic valve, the apparent welding of two cusps together to form a shrunken and misshapen commissure. Among our specimens were a few frank examples of bicuspid aortic valve; but in many others the appearances were less clear, or vegetations confused the picture: there was recurring difficulty in differentiating between a congenitally malformed valve, the seat of healing vegetations, and a valve, originally normal, but now grossly deformed by ulceration and fibrosis. We had begun to suspect that a congenitally bicuspid malformation might be an underlying factor in many of the cases ; and, as this suspicion grew in force, so did the idea that through this particular congenital defect our problem might begin to resolve itself. Thus we came to study intensively the relation of the bicuspid

valve to bacterial endocarditis. In this investigation it was first necessary fully to acquaint ourselves with the architecture of the aortic valves as studied in serial sections of the whole valve, and histologically to compare normal valves and uncomplicated instances of bicuspid aortic valves so as to establish decisive points of identification; thus we became able to differentiate between normally and defectively developed commissures, even though they were deformed by the vegetations of bacterial endocarditis. An outline of these studies, and of the further enquiries and conclusions to which these led, will now be given.

## THE BICUSPID VALVE.

The relative positions of the cusps of the normal pulmonary and aortic valves as seen from above are shown in Fig. 39a. According to the nomenclature that we adopted, the left and right anterior cusps are those from above which the corresponding coronary vessels ordinarily spring; the remaining, or posterior, cusp forms a commissure with the right anterior cusp directly above the membranous septum (*MS*). The three cusps are usually almost equal in size. When the aortic valve is bicuspid, as it proved to be in about 1% of people, any one of the three commissures may have remained undeveloped, but failure of that separating the right and left anterior cusp is much the most frequent. The commissure may fail completely, as in Fig. 39b; or it may be represented by a ridge or bar of tissue, as in Fig. 39c and d.

The complete absence of a dividing ridge or frænum (Fig. 39b), and the absence of an angular break in the sweep of the line of attachment of the larger of two cusps, were used by Osler, and quite rightly, as evidence of faulty growth. But this form of bicuspid valve, while the easiest to recognise, is not the common form. The common form is that in which a ridge or frænum partially subdivides one of two cusps, and such may indicate an inflammatory or a developmental fusion. In the congenital case the dividing line is usually marked by a simple ridge, 1 or 2 mm. deep, and 2 or 3 mm. broad, its almost parallel borders extending from the edge of the sinus well onto the cusp or even to its margin. This ridge may subdivide into smaller diverging ridges as it proceeds. In inflammatory fusion a deeper and often narrower partition is the rule; and it may even be evident at a glance

that two originally normal cusps have been stuck together. These indications are often sufficient to differentiate, where the

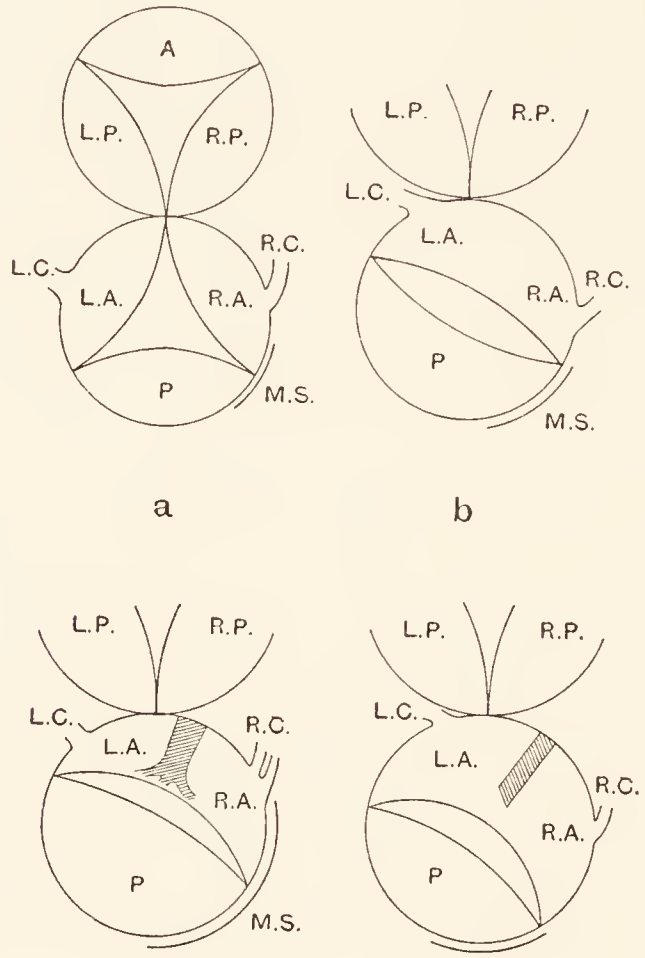



FIG. 39.—Semi-diagrammatic representations of the pulmonary and aortic valves. The structures have been drawn to scale and are reproduced a little less than natural size.

*a*. The normal pulmonary and aortic valves ; the former consists of anterior (A), left posterior and right posterior cusps (L.P. and R.P.) ; the latter consists of left and right anterior (L.A. and R.A.) and posterior (P) cusps. L.C. and R.C. = left and right coronary arteries. M.S. represents the position of the membranous septum.

*b*. Congenital fusion of the left and right anterior cusps of the aortic valve. There was in this instance no trace of ridge or commissure separating them.

*c*. Congenital fusion of the left and right anterior cusps of the aortic valve : the line of fusion was represented by a long, smooth, low ridge, ending in three short branches near the cusp margin. The small size of the fused cusps in this case is a point in favour of developmental defect.

*d*. Congenital fusion of left and right anterior cusps. The separation was marked by a line of small elevations.

All three instances of bicuspid valve here shown were from cases of subacute bacterial endocarditis ; and all three valves were examined microscopically.

valves are uninfected ; but they are much less reliable when the deformed commissure is the seat of fresh disease. It is here that microscopic structure has such value.

IDENTIFICATION OF BICUSPID VALVES.

Ultimately deformities arising from defective growth or from inflammation were differentiated histologically.

The structure of the normal aortic valve may be illustrated by a vertical section passing through the centre of a cusp and radially through the aortic wall (Fig. 40). The foundation of the cusp, its skeleton, is seen to be a thick layer of dense connective tissue, thrown out as a continuation of the annulus fibrosus. This

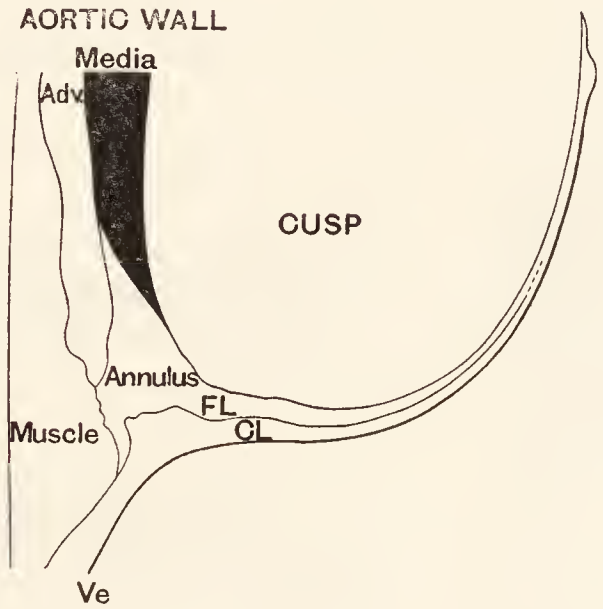



Fig. 40.

fibrous layer (*FL*) runs almost to the free margin of the cusp; it is clothed on its sinus side by a prolongation of the internal layers of the aorta, including the sinus elastic layer; it is clothed on its ventricular side by a prolongation of the internal layers of the ventricle, including the ventricular elastic layer (*Ve*) and a thick subelastic layer of connective tissue (*CL*). The annulus lies in the base of the cusp and may be said to give the latter firm attachment; in the section it is seen to meet the aortic media above in a bevelled junction, the media overlapping the annulus on the inner (cavity) side. When sections are stained for elastic tissue, the media of the aorta, and the sinus and ventricular elastic layers continuing into the cusp stand out prominently, as in the diagram, and are easily recognised. Now the annulus, when examined as a whole, is more than a plain ring of tissue surrounding the base of the aortic orifice; three long tongues of the same tissue project upwards from it in the wall of the aorta and each of these forms the basis of attachment

of one of the aortic valve commissures. The tongue of annulus also meets the aortic media above, but in its whole length overlaps the media on its inner side (Fig. 41*a*). Thus the bevelled junction of annulus and media is in the reverse direction to that previously described as normally found at the centre of the cusp (Fig. 40). This difference in the relation of annulus and media in the centre of the cusp and at the commissure often becomes a crucial observation.

If two united cusps are marked by no distinguishable septum or ridge, and the union is congenital, vertical sections through the centre of the combined cusp show the tissues to be arranged

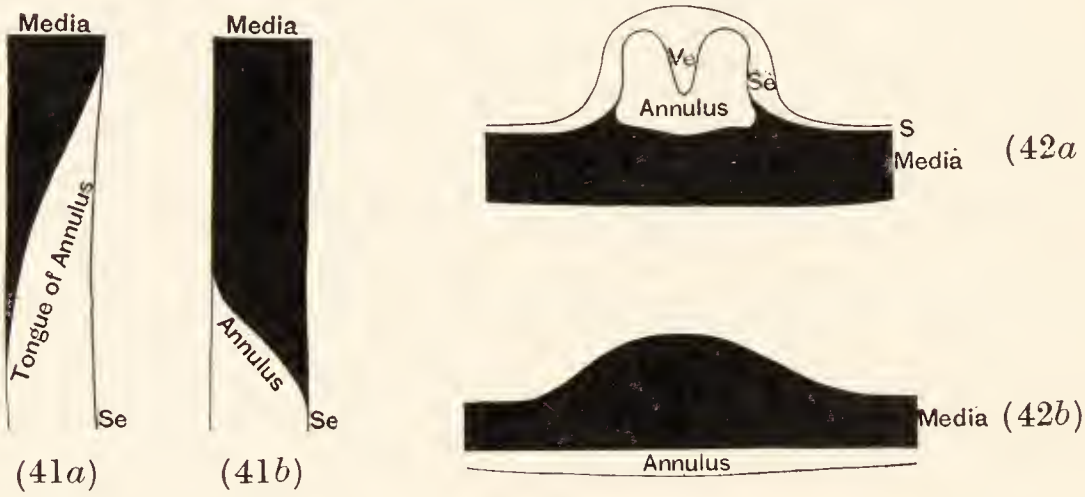



FIG. 41*a* and *b*.—Diagrammatic representations of longitudinal (vertical) sections through aortic commissures, normally developed and congenitally deformed. The diagrams show the different relations between media and annulus in the two instances; the long upwardly directed tongue of annulus intervening between media and aortic cavity in the normally developed commissure (Fig. 41*a*) and the short and reversed overlap, occurring at a lower level, in the malformed commissure (Fig. 41*b*).

FIG. 42*a* and *b*.—Similar diagrams illustrating sections across the commissures. In inflammatory fusion (Fig. 42*a*) the tongue of annulus lies between cavity and media; remnants of the originally separate cusps can be detected within the ridge of fusion and often, as here, the reflection of the sinus elastic layer (*Se*) back to form the ventricular elastic layer (*Ve*) is to be seen. In the congenitally fused ridge (Fig. 42*b*), the annulus lies outside the media. At all levels of the congenital ridge, followed as far as the very margin of the valves, the several layers sweep across from one side to the other without interruption, as is here illustrated.

just as they are in the case of a single normally developed cusp; there is no trace of upwardly projecting tongue of annulus to mark the position of an old destroyed commissure.

If two united cusps are marked by a dividing ridge, section of this ridge will discover its nature; for they will again show

whether this ridge has or has not the tongue of annulus previously described as its foundation. The distinction can be made without difficulty in longitudinal (Fig. 41*a* and *b*) and in transverse sections (Fig. 42*a* and *b*).

These studies provided criteria, enabling us conclusively to identify congenitally bicuspid valves in our own specimens. When correlated with the macroscopic appearances, they afforded very great help to the recognition of similar malformations in valves described in previous records, or seen in museum specimens.

### BACTERIAL ENDOCARDITIS AND BICUSPID VALVES.

First we examined our own material. This consisted of a series of specimens taken from 31 consecutive cases of subacute bacterial endocarditis studied clinically and coming to autopsy. Among these 31 hearts there were 8 (or 26%) showing undoubted bicuspid aortic valves. If those cases in which the aortic valves were only slightly affected or escaped infection were excluded from the total, 20 cases remained in which the aortic valve could be regarded as primarily infected; among these were all the 8 bicuspid valves, constituting 40%. It was recognised that this remarkable figure might prove to be a little too high or too low; but that it does not depart widely from the true value a comparison with other series of specimens, without submitting these to microscopic examination, gave assurance. Thus, amongst a series of 17 unselected cases deposited for many years in the museum of the Royal College of Surgeons, London, no less than 8 instances of bicuspid aortic valve were found. Later observation has not caused us to alter our conclusion that among cases in which the aortic valve is more than slightly involved, a congenital defect, almost as often as not, is the determining cause of the disease. This conclusion approaches, if it does not reach, finality for the group considered; so far as the individual cases were concerned it was founded upon demonstration and not upon opinion. The observations described clearly indicated the very important part played by a relatively simple congenital malformation of the aortic valves in the causation of subacute bacterial endocarditis; they led to the second part of this phase of the enquiry, namely, to the attempt to ascertain how frequently bicuspid valves become infected.

The frequence of fresh endocarditis in cases of bicuspid aortic valves has been commented upon by earlier writers. Although the cases were not described as instances of subacute bacterial endocarditis—the disease being unknown at the time most of the cases were recorded—it was safe for us to regard them as being of this kind with few exceptions. There was evidence in the early reports and illustrations to this effect; and from direct experience acute bacterial endocarditis was known to be relatively very rare in these cases. The frequence of infection was exemplified by Osler's 7 cases, 2 of which manifested active infection; and among Babes' 5 cases, 2 and perhaps 3, and among Vries' 13 cases no less than 6, were similarly affected. Among a total of 101 cases, which were collected and placed in one group after close scrutiny of a larger number, 9% of those dying under 20 years of age showed vegetations; and no less than 23% of those reaching adult life, and there were 69 of these, presented vegetations. In concluding that at least 23% of subjects having bicuspid aortic valves and arriving at adult life acquire infective endocarditis, it is to be recognised that the true percentage is probably a higher one, because the case of bicuspid valve most frequently overlooked is just that in which endocarditis has developed and in which vegetations confuse the picture. But this percentage was accepted for purposes of argument as representative; and it was so large as to demand explanation. That valve lesions might predispose was already recognised, but the precise mechanism of this predisposition appeared not to have received much consideration. It was impossible to call inefficiency of the heart to account in this particular instance, as it might perhaps be called in other forms of congenital malformation, for the bicuspid aortic valve is a very trivial lesion from the functional standpoint. It is true that signs of aortic regurgitation sometimes manifest themselves in the uncomplicated case, but such regurgitation is rare. An inconstant or slight functional defect in the heart could not reasonably be used to explain failure in the defences of the body, or to explain how organisms enter the blood stream and survive. This consideration forced us to accept the alternative idea that the malformed valve predisposes by catching and holding bacteria once they have entered the circulation, and that this entrapment is alone responsible; it

explained the central fact that it is the aortic valve which becomes the seat of disease. The entry of organisms into the blood stream, though a necessary link in the chain of events, could not be considered as determining the disease. But this being so, then it followed that a group of subjects having bicuspid aortic valves could be regarded as affording a minimal index of the frequence with which the blood stream of adults in general is invaded by the organisms responsible for subacute bacterial endocarditis. The figure, as has been seen, is at least 23%. We were brought to conclude, therefore, that at least 23% of adults experience this invasion. But, since subacute bacterial endocarditis is a comparatively uncommon malady, invasions must very frequently occur without mishap. The relative immunity of the normally developed subject is not the result of freedom from invasion by the specific organism, nor is it due to the entering organisms being inadequate in numbers or in virulence, but it is merely due to there being no suitable lodgment. This line of reasoning, which the new facts allowed to be carried through with some approach to decisiveness, threw a new light upon the pathology of subacute bacterial endocarditis.

## THE NATURE OF THE DISEASE.

The subacute variety of bacterial endocarditis is of a distinctive kind. It is peculiar in that, while running to a fatal ending, the course is remarkably protracted. The organism, having gained a foothold seems for long periods unaggressive; the symptomatic reactions of the patient to the organism are inconspicuous in all but the terminal stages of the disease; the tissues react locally, everywhere manifesting signs of partial healing and sometimes of local healing that is complete, though healing proceeding to recovery from the disease is not as yet known to occur except in the rarest cases. The history of the disease in the individual case is that of a long drawn struggle, in which fluctuations in well-being are frequent, and in which the end often comes through such an accident as embolism, or through intercurrent infection, or through renal failure. This picture contrasts with that of acute bacterial endocarditis; in this the symptoms of poisoning dominate, the course is short, local evidences of healing are almost absent, and the patient sinks

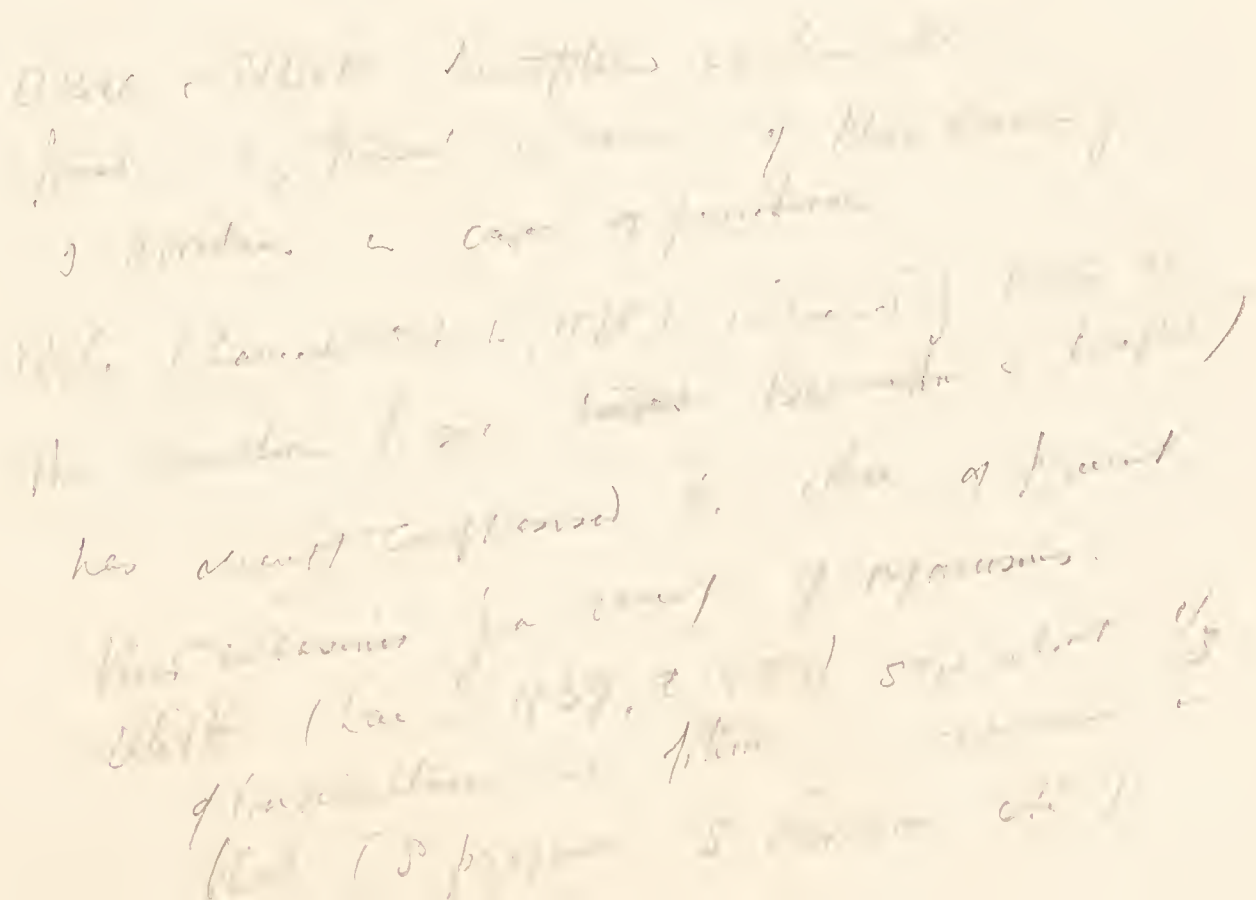
rapidly. For the first type of malady it had now definitely been shown that in a considerable proportion of the cases the pathology is peculiar in that the disease is determined by a local defect. This is almost certainly not so for the acute type of disease ; there is no evidence of any particular predisposition of bicuspid aortic cases to this infection, which affects the valves of the right as frequently as those of the left side of the heart, which is most often pneumococcal or staphylococcal, and takes the form of an almost unresisted septicæmia. By common consent subacute bacterial endocarditis almost always results from the non-hæmolytic green streptococcus, a slow growing and weakly pathogenic organism, first found associated with the disease by Schottmüller. The more virulent infections require no help from structural defect ; the less virulent, judging from the case of the bicuspid valve needs a point of lodgment. Thinking along these lines, the association of a peculiar pathogeny and peculiar course in the subacute disease seemed natural ; and infection of the kind being known to settle down upon other forms of chronic heart mischief, such as mitral stenosis, it appeared well within possibility that all subacute cases are secondary to antecedent defects. The view to which we came is that in subacute bacterial endocarditis generally, the organism responsible is of a kind to which the body is accustomed before the valve becomes the seat of its multiplication ; that invasions are frequent, that in the fight for dominance there is almost a balance between organism and defence, and that only because the valve offers to the bacteria a suitable redoubt are they able to entrench and establish themselves. Such a conception, especially as it permitted the idea of reinfection and even repeated reinfection at short intervals to be entertained, made the origin and behaviour of the disease much more intelligible. Grant, Wood, and Jones subsequently searched for a common type of lodgment and concluded that it is not the deformity itself which matters, but the demonstrable proclivity for this and certain other forms of valve defect to become the seat of minute platelet thrombi.

These researches upon subacute bacterial endocarditis have been chosen for inclusion in this book, not so much to show the value to clinical science of an appeal to morbid anatomy, for that is obvious ; they are included to illustrate how this appeal is

inspired and the work directed by studies of the same patients during life. For it was interest in the living, and the attempt to find a guide to the peculiar insidiousness of the disease as witnessed in the patients, which stimulated the close examination of their hearts after death, as has been described at the beginning of the chapter. And the correlation between the lethargic course of the malady and a peculiar pathogeny, while essential to the argument, is probably fundamental to a true understanding of the development of the disease. Future additions to knowledge of the origin of this interesting malady will probably come chiefly through bacteriological channels; not from purely laboratory studies, but from clinical investigations of the times and channels of streptococcic invasion.

The development of the investigation also illustrates a point difficult to stress unduly, namely, that the success of investigation often turns upon the gathering of precise information relating to what might be judged recondite or even unpromising detail; in the present instance it turned upon study of the intimate structure of bicuspid aortic valves, rendering these recognisable with certainty. It was this work that gave confidence to the studies relating the frequence of endocarditis to this congenital malformation of the valves and to the idea of frequent invasion of the blood stream by the specific organism. The necessary confidence had previously been lacking, though the idea that subacute endocarditis may at times be superimposed upon old standing fibrosis of valves had long been considered and was even accepted by many people.

NOTE.—The original accounts of these investigations, and relevant references, will be found in Lewis and Grant, *Heart, Vol.* X, *p.* 21, and Grant, Wood and Jones, *Heart, Vol.* XIV, *p.* 247.



# CHAPTER 13.

## "RAYNAUD'S DISEASE."

### EARLY WORK.

In 1862, Raynaud collected a number of his own and of previously recorded cases into one group in a paper "On local asphyxia and symmetrical gangrene of the extremities"; the group became the basis of what is now generally termed "Raynaud's disease." In this and in his subsequent publications he wrote of local "syncope" as the simplest form and described it as occurring ordinarily in females and consisting of attacks, often determined by exposure to cold, in which fingers, and sometimes toes, become pale, cold, and numb. In the more pronounced cases pallor is replaced by cyanosis, and swelling and pain are frequent; in still more advanced cases symmetrical gangrene occurs, appearing as small blisters and ulcers on the tips of the digits and leading to the detachment of small areas of skin and to the formation of little hard depressed cicatrices, the digits tending to become slender, tapering, hard and parchmentlike. He described these types, not as distinct, but as constituting degrees of one malady.

The term "Raynaud's disease" remains to this day without final definition. For the moment we may accept his view that the simpler and the graver forms, selected for description here, are examples of one disease. It is certain that in cases presenting the more serious symptoms these have usually been preceded by attacks merely of discoloration; but the simple syncope does not inevitably develop with time into the severer form; the development of the malady is variable and the homogeneity of the group is not to be accepted without reserve.

It may be well to ask in the first place, what Raynaud actually accomplished? His was the earliest description of a group of

cases, and his general account of symptoms and signs was full and accurate. He definitely showed that the cases he was describing are to be distinguished from cases of gangrene resulting from gross disease of main arteries such as that which comes from embolism, or thrombosis, or from senile processes. He established the attacks as due to transient loss of blood supply. He stated his belief that the small arteries are involved in this spasm and in this belief he has since been proved to have been right. The belief, which he also expressed, that the spasm comes through an irritable condition of parts of the central nervous system (he said cord) presiding over vascular innervation, was, as we shall see, ill-founded. It is an instructive fact that Raynaud's view of the vasomotor origin of the malady has remained almost unchallenged until quite recent times, although the evidence he brought in support of his theory was of the slightest kind. The history of "Raynaud's disease" illustrates how, under the method which merely observes phenomena as they present themselves, an accurate description of the events often comes to be accepted almost as an endpoint; and how under the same system the addition of any explanation, apparently covering what is witnessed, satisfies; the hypothesis is submitted to no critical tests. Although accurate descriptions of the simple phenomena of disease are invaluable, the purely observational method soon becomes exhausted; actually Raynaud himself almost exhausted it in the instance under discussion. When my own interest was aroused in these patients, and past writings were closely searched, it seemed apparent that progress by the observational method had been brought to the point of standstill. But it was manifest that the existing evidence for *arterial* spasm was inadequate, and for the vasomotor origin of this spasm almost non-existent; and it did seem clear that these problems could be attacked at once and successfully by means of the experimental method; under this method attempts would be made to provoke and to relieve attacks of discoloration of the patients' fingers, under controlled conditions, varying the tests, and thus more accurately defining the factors determining change, and reasoning from these about the mechanism of the disease. A brief account of this work will now be given.

The attempt artificially to induce attacks of discoloration in the fingers of predisposed people resolved itself chiefly into a

study of reactions to cold, which was generally recognised to be the chief determining agent in spontaneous attacks. The patients chosen were not of the mildest type, but those who very frequently presented spontaneous and bilateral attacks of discoloration of the fingers in cool or cold weather, for it was correctly anticipated that attacks could be induced most readily in these; some gave the history or showed the signs of small areas of necrosis of the finger tips, or tightening of the skin, others did not. In attempts to induce attacks, initial difficulties were experienced; these were due to ignorance of the actual temperatures most suited to their production, of the necessary time of exposure, and of other factors. These initial experiments and failures will not be described. It was not until the temperature of hands had been closely studied in a number of unprovoked attacks that success was attained. The fact that, while a certain degree of coldness of the hands is essential, a temperature not very much lower causes a vasodilator reaction in the hands (*see* page 96), which actually prevents an attack occurring, was unknown at the time, and was responsible for much preliminary disappointment. Ultimately it was found that immersion of the hands in water at about 15°C., for periods of about 15 minutes in cool rooms, usually brought the bloodflow in the affected fingers to an end, and in many of the patients with regularity.

### EVIDENCE OF ARRESTED BLOODFLOW.

At the time the investigations began, it was generally held that in attacks of full discoloration of the skin, of waxy whiteness or of deep cyanosis, the bloodflow to the skin has ceased. That conclusion seems to have rested upon the interpretation of the discoloration and upon the very occasional observation that, when discoloured, the skin if pricked or cut refuses to bleed. It had also been said, and this was easily confirmed, that microscopic examination of the skin at the base of the nail showed the blood to be standing at rest in the capillaries during such attacks. A further evidence was the development of numbness in the discoloured fingers; but this could not be used effectively so long as it could be attributed to disturbance arising in the nervous system. The latter explanation was early excluded, the numbness being shown to be the effect of loss of bloodflow. Later experiment

showed that the normal finger becomes numb in exactly the same way, namely, at its tip with spread towards its base, when artificially deprived of its circulation; and the time taken for numbness to develop in the normal finger after the bloodflow to it is deliberately obstructed, or in the finger of a patient after an attack is started by cooling was found to be the same, provided that the temperatures of the fingers are maintained at the same level in the two instances.* Since it is impossible to assert from microscopic examination of the skin that there is absolutely no flow in any of the vessels at any given moment, the regular occurrence of numbness in attacks that are prolonged becomes a chief evidence; the numbness indicates that the nutrition of the sensory nerves is greatly impaired and that any flow of blood that is still occurring in the skin is so minute as to be negligible. Thus it may be accepted that the circulation has ceased in those attacks in which the fingers display waxy pallor or full cyanosis, meaning by full cyanosis the final cyanotic tint displayed by the skin, when by artificial means the flow of blood to it has been prevented completely. Owing to the delayed onset of numbness, the development of this full cyanotic tint becomes in experiment the usual criterion of completely obstructed bloodflow; it is a criterion that is quite reliable when the finger is cool or cold (15° to 20°), for at such temperatures, owing to the small amount of oxygen given up to the tissues, a very slight movement of blood in the vessels suffices to keep the skin pink.

The conclusion that the circulation to the skin is brought to an end in the attacks being consolidated, the next step, was to determine what vessels close spasmodically.

## VESSELS INVOLVED IN SPASM.

The occurrence of deep cyanosis of the skin in many of the attacks had suggested to some observers that the vascular spasm might be on the venous and not on the arterial side, and this idea received support from the undoubted fact that in the attacks the veins beneath the skin shrink in size and become almost or quite invisible. That this diminution in the size of veins might be the simple and normal consequence of their increased contraction in direct response to the coldness of the hand, was

* See Lewis, Pickering and Rothschild, *Heart*, *Vol.* XVI, *p.* 12.

overlooked; and the oversight well illustrates the danger of neglecting control observations. The hands are always cold in the attacks and the veins of normal hands shrink similarly in the same circumstances. Actually it was soon proved that, despite the smallness of the veins, they are still patent. If during a spontaneous attack of full cyanosis the hand is raised, the depth of skin colour decreases, and if the hand is lowered it increases, a clear and simple demonstration that the venous channels are open. Later when Dr. Landis came to work with me, I suggested that he should measure the actual pressure in the capillary loops of the finger during the attack by means of his very exact capillary manometer. He did so and found the pressure to be lowered during the period of the attack.* He also showed that if a pressure of 40 mm. is thrown into a pneumatic cuff upon the upper arm, the pressure in the capillaries rises very gradually, owing to the very slow filling of the veins; but when the pressure has reached cuff pressure, release of the latter is followed by an abrupt fall of capillary pressure, as the blood flows out of the capillaries and venules into the now unobstructed veins. It was abundantly proved by this series of experiments that in the attacks in which the fingers are cyanosed, there is a free outlet from the minute vessels of the skin to the main veins of the arm.

Investigations turned to the arterial side, the hands being examined first during unprovoked attacks of full cyanosis. Observations showed the radial pulse to be palpable even in attacks in which the hand was discoloured to the level of the wrist. The pulse is often small during attacks; though this cannot be said to be significant, because the pulse normally becomes smaller when the corresponding hand is cold. It is possible that the radial and ulnar arteries narrow unusually in attacks affecting the whole hand, but the actual obstruction is in smaller vessels. When in an attack the circulation to the skin of the fingers, with or without that to parts of the hand, has come to a standstill, as shown by corresponding areas of full cyanosis, the vascular spasm can be relieved and the hand restored to a fresh pink colour by soaking it in warm water (about 40°) for 3 or more minutes. By exposing different parts of the hand to warmth in this way much was learned about the vessels involved

* Landis, *Heart*, *Vol.* XV, *p.* 247.

in the spasm. If the distal half of a finger, showing cyanosis in its whole length, is immersed and retained in the warm water, its tint does not change, though the colour may deepen a little; this is the case however long the immersion continues, provided that the rest of the hand is kept cool. The vessels of the skin below the water line dilate in response to the warmth, but no fresh arterial blood is able to enter the finger; that is so because the obstruction is not in the arterioles of the skin but in vessels of the order of the digital arteries, and these remain contracted above the water line. If the palm of the hand and roots of the fingers are immersed in warm water, the cyanosed fingers being kept above the surface of the water in cool air, the bases of the fingers soon become pink, and the pink colour gradually spreads up the finger till the circulation is restored to its whole length. In this experiment the palmar arteries and the digital arteries at their origins become dilated, allowing warm blood to enter the bases of the fingers; this warming of the fingers at their bases relaxes the digital vessels in the adjacent and slightly more distal part, the process being repeated until gradually the vessels open in the whole length of the fingers. If the distal half of the finger has been warmed previously, then subsequent warming of the base of the finger causes an abrupt restoration of bloodflow to the finger in its length. These are the experiments demonstrating that when the whole finger is cyanotic the spasm actually affects arteries of the order of the digital vessel and affects these, not at one level, but in the whole length of the finger.

Confirmatory and additional evidence regarding the vessels involved was obtained by local cooling of hands while free from the attack. In sufficiently susceptible subjects the immersion of one or two fingers in water at 15° for 10 or 15 minutes brings cyanosis in these and in these only. The area becoming discoloured is less, by about the length of a phalanx, than the area immersed. Thus, if the distal half of the finger is immersed, cyanosis appears only over the terminal phalanx. If the finger becomes affected at all, its tip is always discoloured. This distribution again provides evidence against spasm either of minute vessels or of cutaneous arterioles being concerned in bringing bloodflow to an end, and once more indicates the digital arteries. Assuming that these vessels contract to the water line, and that their branches arising

a little higher and proceeding down below the water line are unaffected, the distribution seen is the expected one. If the palm of the hand with the base of the fingers is cooled, the rest of the fingers being kept warm, the fingers soon become cynaotic. In some subjects it is sufficient to cool the palm of the hand at the base of the little finger to render this finger cyanotic in its length. The distal parts of a finger can be rendered cyanotic by circulating water around the middle third of the finger. These are the experiments demonstrating that the circulation to the finger can be stopped distally by cooling the palm of the hand or any part of the finger in its length. They showed the susceptibility of all parts of the corresponding digital artery to the direct effect of cold.

### ORDER OF INVASION AND RETREAT.

In spontaneous attacks of cyanosis, the portion of the finger affected is its distal part, the tip, the last phalanx, the last two phalanges, or the whole finger. The discoloration may come over the whole finger simultaneously; much more usually discoloration comes at its tip and spreads up the finger; recovery occurs in the reverse order. It is the rule, to which there are no important exceptions, that if a proximal part of a finger is discoloured, so are its more distal parts (Fig. 43). The explanation of these events was given by the experiments already described. When a hand is exposed to cold out of doors, the arteries first to experience cold of sufficient degree are those of the fingers, and especially of the distal parts of the fingers, since the blood is cooling as it travels, and the ends of the fingers lose heat quickest. Longer exposure will involve a greater length of the artery in the finger and eventually the same vessel may suffer in the palm. Thus the phenomena observed in unprovoked attacks are adequately explained if we suppose that arteries of the size of the digital vessel close to obliteration when cooled to a certain critical point. The artery first experiences this critical temperature in its distal part and, as exposure lengthens, the temperature of more protected parts of the vessel falls to the critical level and more of the finger becomes implicated. The manner in which the attack comes in response to general exposure, or to simple immersion of the hand in cold

water is the same. This orderly invasion, and the reaction of limited parts of hand and finger to cold, did not seem compatible with the view, which was current at the time the observations and experiments were made, that the vascular spasm is a vasomotor phenomenon. There was no reason to suppose that vasomotor impulses, when only weakly aroused, confine themselves to the tips of the fingers, and that their influence spreads in stages up the

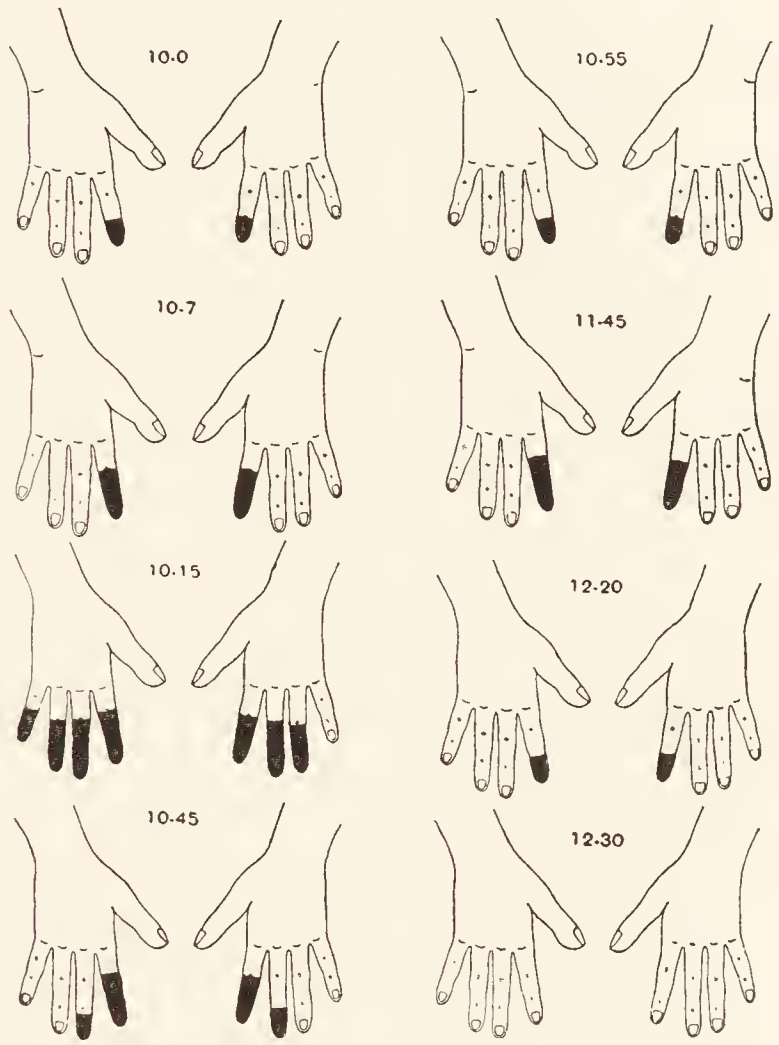



FIG. 43.—An attack of cyanosis in the fingers of a case of "Raynaud's disease." The times of day (corresponding to the progress of the attack) are given. Cyanosis began symmetrically in the tips of the index fingers and spread up these fingers. Eventually it similarly involved other fingers, the thumbs escaping. In the recovery, once (11.45) temporarily interrupted, the order of events was reversed.

hand as the impulses become stronger. Evidence from animal experiment indicated general and equal contraction of the vessels over the whole field involved. The vasomotor origin of the attacks was also most difficult to accept in view of the demonstration that the vessels of a single finger or of a part of a finger could be thrown into spasm by quite local cooling and relieved by quite local warming. No physiological sanction could be found for

a notion that vasomotor effects can be reflected exclusively to the small area in which the stimulus arises. The evidence pointed to a direct action of cold upon the vessels and not to an indirect action through the nervous system, and led to a critical revision of previous, and to the collection of fresh, evidence.

### BLANCHED FINGERS.

Blanching of the fingers in the attack was believed by Raynaud to result from spasm of the capillaries, and it was to this first that he applied the hypothesis of disordered innervation. The significance of blanching is that it does not follow passively upon simple arterial occlusion and that vaso-constrictor impulses can cause the minute vessels of the skin to contract to obliteration, as recent work has proved.* The importance of ascertaining the origin of blanched skin in the attacks will be apparent.

It is frequent for patients to state that the order of colour displayed in the attack is first whiteness, then blueness, and finally redness in the stage of recovery. But in a very large number of attacks witnessed by us from their beginnings, blanching has never been the first event ; the fingers first become cyanosed. The discrepancy is probably due in part to the circumstances in which the attack occurs. The patient speaks of attacks coming on while the hands are in use ; the attack that is witnessed happens while the hands are at rest. If the flow of blood through the arteries stops and the hands continue to move, the vessels tend to be emptied by this movement. Blanching so produced is passive, and is often incomplete. A patient notices first that fingers, which are being used, are becoming numb ; she looks at them and sees them pale ; out of such experience comes the statement that the fingers become pale and numb suddenly. It is the observation and not the event that is sudden. Fingers do not become anæsthetic until the circulation has long been lost in them ; the early and slight changes of tint are not observed and the patient has no knowledge of when the blood flow stops. If the moving fingers that are pale are brought to rest, the patient allowing the hand to hang down, the fingers often and promptly become cyanotic ; chiefly from this source comes the incorrect statement that pallor precedes

* See Harris and Marvin. *Heart, Vol.* XIV, *p.* 135.

blueness. The discrepancy between the patient's statement and what is observed, and the confusion, which has in fact occurred through too free acceptation of the former, illustrates how important it is to go and see, and how unsafe it may be to rely upon the hearsay statement.

Speaking of attacks observed from their beginnings, blanching of fingers until they are uniformly waxy in appearance has been witnessed only after the circulation has become arrested for many or very many minutes. This waxy pallor, which directly replaces full cyanosis, whether this full cyanosis is faintly expressed or conspicuous according to the blood content of the skin, is in fact due to active contraction of the minute vessels, as the following evidence demonstrated to us. The waxy area is sharply marked off from the coloured skin of the more proximal parts of the hand. If the venous pressure is now raised artificially in the limb, say to 40 mm. Hg, the minute vessels do not fill but withstand this pressure, or filling they do so in a peculiar and significant manner. The sharp line that separates cyanosed and waxy skin moves very slowly down the finger; the pressure in the minute venous plexuses being raised in the congested skin at the margin of the pale area, the resistance of the corresponding vessels in the pallid area is gradually overcome and little by little they give way. The arterial spasm is not relieved, the entry of blood is from the venous side. In such tests the pallor may be driven completely from one finger, while in another it remains unaffected. If the venous congestion is now released, the finger that has passed from the pallid to cyanotic condition remains cyanotic; it does not pale again promptly, as it would do if the capillaries were contracting in response to continuously increased vasoconstrictor tone. The explanation put forward to account for the waxy pallor, which behaves so peculiarly, is that it is of the same nature as that seen in the body after death or in Bier's spots*; the precise mechanism of this blanching is unknown, but it is known to be local, to be independent of the nervous system, and to appear when the circulation to the skin has been brought for many minutes to a standstill. These, briefly stated, were the observations and arguments, which showed that waxy pallor

* For an account of which see "*The Blood Vessels of the Human Skin and their Responses*," *London*, 1927.

is not the starting point of an attack, and that it is unnecessary to invoke vasoconstrictor impulses to explain contraction of the minute vessels of waxy fingers, for it is a natural though an active sequel to arrested blood supply to the skin. We proceed with the main question.

### VASOMOTOR HYPOTHESIS.

It is a matter of interest to realise how the hypothesis of vasomotor overaction came to be applied. The true reason why Raynaud attributed the attacks to disordered innervation is that this explanation was brought to his mind by contemporary physiological work. His view was first put forward in 1862, only a few years after the vasoconstrictor nerves were discovered; vasomotor centres were announced in the mammal in 1874, and in that year Raynaud published his second paper and introduced them as an addition to his hypothesis. Having excluded gross disease as a cause, having shown the malady to be spasmodic and yet not the result of ergot, the new idea of disordered innervation was there to his hand and he used it, naturally enough though precipitately. The incident carries its own warning; the overaction or underaction of some bodily function may be capable of explaining a clinical phenomenon, but that is an insufficient reason for adopting the explanation. Raynaud was aware of this, and in his first paper urged in support of his view that the vascular spasm occurs in subjects characterised by a nervous predominance, young women, hysterical people, and children. When Raynaud's thesis came to be considered, this form of argument seemed much too indirect to be acceptable, as also did the argument of many later writers that "Raynaud's disease" is specially associated with various diseases of the nervous system; actually the statements of fact would not withstand critical examination. In his second paper Raynaud added the further argument that galvanism applied over the vertebral column modifies the asphyxial state of the extremities, and that this treatment brings about favourable results by weakening the excitomotor power of the cord. That this form of treatment has long since been abandoned is a sufficient comment. These arguments could command no serious consideration, and no more substantial evidence appeared to be forthcoming. With the exception that attacks may be determined

by emotion, a fact specially to be considered later, what has here been reviewed is the evidence upon which the vasomotor hypothesis rested for so very many years. It is true that Raynaud believed he saw transient contractions of the retinal arteries in certain of his cases; it brought him, so he thought, direct evidence of arterial spasm; and it has helped to give credence to the vasomotor hypothesis. Actually, when Raynaud's original case reports, and those brought forward later by others, were critically studied, it became impossible to accept as fact that spasm of the retinal vessels has been witnessed in this malady.*

Such then was the position when the question was reopened. Resort was had to anæsthetisation of the ulnar nerve. Physiological experiment had shown that the vasoconstrictor nerves pass to the vessels of the limb in the mixed nerves and that, at least so far as the peripheral parts of the limb are concerned, this is their exclusive path. In the normal hand anæsthetisation of the ulnar nerve gives full vasodilatation of the vessels of the 5th finger; even when this finger is previously cold it becomes hot; there is no reason to doubt that all vasoconstrictor supply to this finger is lost when the finger becomes numb and its muscles paralysed. It was found in several of the patients that ulnar anæsthetisation, undertaken when the circulation to the finger was at a standstill, had but little effect in relieving the spasm of the vessels. The little finger, previously cyanosed, remained unchanged in colour, or more usually became pink. But the development of pinkness was long delayed and was accompanied by no appreciable rise of temperature, indicating that only a slight relaxation of vessels had occurred. This failure promptly to relieve the spasm gave conclusive evidence that the latter is not the result of increased vasomotor tone. Further it was found that during ulnar anæsthesia in which redness of the finger reappeared, cyanosis could be restored to the finger by appropriate cooling. In the same connection it was pointed out that after extirpation of the inferior cervical ganglion, undertaken for the treatment of the malady, the circulation to the fingers may still be brought to a standstill by cooling them. Such an effect is clearly and entirely independent of the vasoconstrictor impulse.

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* This aspect of the matter, and that of the supposed association of "Raynaud's disease" with various nervous diseases, is discussed fully in the original papers.

### RÔLE OF THE VASOMOTOR NERVES.

The evidence from anæsthetisation of the ulnar nerve and from cases of sympathetic ganglionectomy pointed again to the conclusion reached by the experiments upon local cooling previously discussed, namely, that a local fault of the vessels, and not an abnormal vasomotor impulse, determines closure of the digital arteries in attacks induced by exposure to cold. It is important clearly to understand the parts played in this circumstance by two factors in bringing about complete closure of the arteries. When cold acts on the body generally, it influences the state of arterial contraction in two ways ; it causes a general increase of vasomotor tone, and by acting directly on the vessel wall causes contraction of its muscle. Both the indirect and the direct actions happen in normal people, and in these together produce a high grade of contraction in the digital arteries. The actions are similar in the case of "Raynaud's disease," but in these there is an abnormal element ; so that the combined action results in a spasm of the artery with occlusion of its lumen. In considering the pathogenesis of the malady, we are concerned only in determining the abnormality. Because an abnormal state of contraction persists in the arteries, or can be induced in these by local coldness, after the vasomotor nerves have been paralysed, we rightly and finally conclude that the abnormality is local. But in considering the behaviour of the fingers both factors must be taken into consideration. Thus, when the arteries are in a state of spasm, they become more relaxed when the ulnar nerve is anæsthetised, and ablation of sympathetic ganglia tends to prevent spasm developing in the affected area and in mild cases may be sufficient to stop attacks of cyanosis occurring. But these are the anticipated results of loss of normal vasomotor tone ; they provide no evidence of abnormal nervous impulses. The only factor shown to be abnormal is the local one and this suffices to explain all the known facts. It would be irrational to recognise vasomotor tone as a causative factor unless it were proved to be abnormal in degree.* The point discussed is highly important to clear

* Efforts, and there have been a number both by others and in my laboratory, to ascertain by measurement if the contraction of the vessels to a central stimulus is more than normal or not in these patients, have so far failed to be convincing, though pointing in the direction of normality. The practical difficulty is that the size of the vessels before applying the stimulus is unknown. It may be of interest here to note that there is no significant change of blood pressure in the attacks.

thinking; and, as it enters into the consideration of other problems, may be illustrated further. An almost parallel instance occurred many years ago when the manner in which digitalis acts in auricular fibrillation was debated. It was found that if the rate of ventricular beating is slowed down by means of digitalis, the original rate can at least be restored by giving atropine, and from this it was concluded, and incorrectly concluded, that digitalis slowing results purely from an action of digitalis upon the vagus nerve. As it proved, the correct conclusion is that the quickening under atropine is due, largely or wholly, to abolition of normal vagal tone, the tone present before digitalis is given. Similarly it may be said that sympathectomy abolishes the normal vasoconstrictor tone, the tone that is present before the disease begins. To show that digitalis slowing is purely vagal in origin, it would be necessary to show that atropine quickens the pulse to the same point as it does when no digitalis has been given; to show that arterial spasm is entirely vasomotor in origin it would be necessary to show that sympathectomy brings the vessels to the same state as it brings those of normal people; this it does not do.

Although it is concluded that the fault is a local one, it is to be anticipated that an attack of cyanosis may be precipitated in cool fingers by a natural increase of vasomotor tone. Experimental tests have demonstrated that this is so. Attacks of cyanosis brought on by immersing a hand in cold water are more easily induced when the body is kept cool than when it it kept warm, for this warmth is associated with relatively low vasomotor tone. If the digital vessels are reacting directly to cold and their lumina are narrower than normal for that temperature, such an increase of vasomotor tone, as is natural as a reaction to cooling of the body, may suffice completely to close these vessels and thus to induce an attack. But attacks cannot be induced even by severe and prolonged cooling of the body if the hand is kept warm throughout (30° to 35°); this in itself shows that even powerful vasomotor tone such as is induced by cold applied to the body cannot alone induce attacks in these patients. In the same fashion, as in the case of cooling the body, sudden pain or an emotional disturbance will sometimes precipitate an attack. Without the intimate knowledge of the malady, which we now possess, and of the precise circumstances

in which such reactions to emotion occur, it was natural that these attacks should have been interpreted incorrectly, and that they should have been attributed to an abnormal increase of vasomotor tone, and not to their rendering effective a narrowness of arteries already present but concealed.

### THE LOCAL FAULT.

The evidence which proved the fault to be local has been given; we come briefly to discuss its nature. Here discussion is admittedly still largely in the stage of hypothesis; but it may indicate lines for new work.

It is legitimate to carry conclusion to this point, that there is a disease in which the condition of the digital arteries is peculiar and displays itself in a direct reaction of these vessels to relatively low temperature, which brings them to a state of occlusion (with intervening periods of full relaxation to an apparently normal state or with intervals of incomplete relaxation), accompanied, according to its duration, by discoloration of the digits and by nutritional changes in them.

At the time of my first publication, the view was held that the peculiarity of the vessels consists of a change in them rendering them unusually susceptible to cold. Delicate records of the pulsations in the fingers at different temperatures indicated that, in the milder cases of the disease, the arteries and arterioles are capable of full expansion throughout their length; only in the severer cases did full expansion fail sometimes to be indicated. Further work suggested that intimal thickening of the digital arteries may play its part, it being supposed that an ordinary increase of tone, which fails to close a normal vessel, may bring or help to bring the diseased vessel to occlusion. Evidence of the actual state of the vessels is still meagre, but most of those examined have shown distinct structural changes. Actually it is uncertain how far moderate grades of intimal thickening would help to induce complete occlusion; it is possible that closure necessitates the development of an unusual tension in the arterial wall. There are cases of thromboangeitis of the arteries of the hand or fingers, in which, as judged by their small capacity to expand in response to local warmth, the vessels are in a state of far more advanced disease than can be those of

many severe cases of the malady here considered. The fingers in certain of these cases may become cyanosed when exposed to cold, but may not be brought to an actual state of closure by this means. This evidence tends to support the original idea that an unusual reactivity of the wall of the artery constitutes the fault. The interesting question has also been raised, as to whether or not long continued or frequent spasm of arteries can lead ultimately to their structural disease. How far structural change contributes to circulatory obstruction in the attacks, and what are the causal relations existing between diminished flow and arterial disease, and between arterial disease and increased reactivity, are questions still unsolved. But the answers to these cannot influence the answer, which is given to the question here chiefly considered, namely, that the condition investigated is not a vasomotor malady but that the fault is a local one.

## WHAT IS "RAYNAUD'S DISEASE"?

The investigations discussed in this chapter have brought certain conclusions. To what do these apply? It is not a trivial question, but one concerned with accurate definition of disease, and the attempt to answer it points the way to further investigation. Do the conclusions apply to "Raynaud's disease"? The question at once raises another, namely, what is "Raynaud's disease"? To this we can only reply, it is what Raynaud described. But Raynaud's collected cases were of different clinical types; his group included mild cases and cases having more severe symptoms, with or without dry gangrene. The nature of many of them will always remain doubtful, so that such a definition is untrustworthy. Strictly speaking, the conclusions that have been reached are applicable only to my own patients, for upon these only were the relevant tests made; these were cases of symmetrical and paroxysmal discoloration of the fingers of moderately severe type; it would not be justifiable to apply them to any other cases than those which could properly be regarded as examples of the same disease. The conclusion formed will apply to such cases of simple syncope as are proved to be earlier or milder instances of the more severe malady. It is conceivable that there are cases of transient discoloration of the fingers, which are due, not to a local fault as

has been proved for some, but to excessive vasomotor tone. This is conceivable, but it is highly improbable, for the assumption of a local cause would readily explain all that we know of both mild and severe type. But if there are these two causes, then there are two diseases, which simulate each other closely but which must be separated and individually named. It is not permissible to take the view that, since the state of a peripheral arteriole is partly controlled by vasomotor tone and in part by a local factor, there can be one disease in which either vasomotor or local factor may be in excess. It is abnormal for human arteries to be rendered impervious either by high vasomotor tone or by the local action of cold, or by both factors acting together. Closure definitely implies an abnormal factor and this might be either vasomotor or local, but not both in one patient.

NOTE.—A fuller account of the experiments and observations here described will be found, with references, in the following papers : Lewis, *Heart*, XV, p. 7 ; Lewis and Landis, *Heart*, XV, *pp.* 151 and 329 ; Lewis and Pickering, *Heart*, XVI, *p.* 33 ; Lewis, *Brit. med. Journ.*, 1932, ii, *p.* 136.

# CHAPTER 14.

## ERYTHRALGIA.

### "ERYTHROMELALGIA" AND THE VASOMOTOR STORM.

As early as 1872 Weir Mitchell described under the term "erythromelalgia" a condition which he believed to be "a rare vasomotor neurosis of the extremities." It came to be regarded generally as a disease, though some writers dissented from this view. Disease or not, the condition has remained undefined and therefore intangible. To speak more generally, unless its pathogenesis is clear, it is almost impossible to define a disease except, as in defining biological species, by a group of symptoms or signs, which are supposed when taken as a whole to distinguish it. But diseases often vary greatly in their manifestations and there is no agreement, and little or no attempt to reach precise agreement, as to what manifestations are required or shall suffice to distinguish. In other words, for many diseases there are as yet no definitions. We may ask, what is erythromelalgia? No precise reply can be given. Mitchell, in first using the term, recorded the symptoms and signs in a group of cases, varying considerably one from another. His general description was a form of compromise; it was not even an accurate synopsis. Others who afterwards used his term also failed to define it and included under it an even greater variety of cases; there is quite inadequate evidence that Mitchell's cases, or those described subsequently, belong to a single class and can properly be regarded as illustrating one disease, an entity. Nevertheless the term "erythromelalgia" has persisted as a diagnostic term under which, as its derivation indicates, certain cases presenting *painful redness of the extremities* are still described. Now, painful redness of one or more limbs, is known to be common to a variety of obviously distinct maladies, but the additional

criteria requisite to bring the case within the class erythromelalgia cannot be stated. The most we can do in attempting to gain general assent is to write down a statement like the following. There are cases presenting a chronic picture of painful redness of one or both feet (or exceptionally hands), in which burning pain is brought on by exercise or by warmth, and in which the foot (or hand) becomes deeply congested and painful when it is allowed to hang down, and in which pain is relieved by elevating the limb or by cooling it ; this is a condition, which is thought to deserve the name "erythromelalgia." The disorder has been vaguely regarded by many as a "vasomotor disorder" or "vasomotor neurosis," whatever these terms may mean, because during periods of pain the affected part is usually found to be hot, it being generally assumed that this heat is the result of a "vasomotor storm" and vasodilatation a primary manifestation of the "attack." Another idea that has prevailed widely and helped to confuse the issues is that a "vasomotor storm" sets in when the limb, usually the leg, is allowed to hang down.

## EVIDENCE OF VASODILATATION.

My interest in this supposed malady was first aroused by reading the very definite statements that were current in relation to the attack of vasodilatation, and especially in response to posture ; search was made in past records to discover the source of the statements and the actual evidence for them. The source of the statements was clearly Mitchell's original paper, but evidence that I could accept as satisfactory could be found neither in his writings nor in those of later workers. It was apparent that Mitchell relied almost entirely upon an observation of his own upon a sailor, whose feet became deeply suffused when hanging down, and in whom pain, redness, heat and throbbing arteries were observed after the man had walked on tender feet for an hour. Mitchell manifestly regarded reddening of the feet on dependency as an evidence of vasodilatation in them, and consequently failed to discriminate between the different significances of reddening and of heat. It was already known to me that normal feet assume a greater depth of coloration when they pass from an elevated to a dependent position, and that

this change may be much more conspicuously displayed when the minute vessels of the skin have been altered and possess little tone. Such a change can be produced locally by any inflammatory affection of the skin lasting several days, as for example, that produced by ultraviolet light. The change in colour is due purely to a passive change in the size of the vessels consequent upon a hydrostatic change in the pressure within them ; this is a physiological result of posture and is usually accompanied, and for similar reasons, by swelling of the veins. It is not vasodilatation, if we use this word in the sense that implies an active change and an increased blood supply to the part, a meaning that is usual and to which I shall here adhere, for it is unaccompanied by an appreciable rise of temperature or by measurable increase of heat loss from the foot. But the fact that Mitchell and his successors had used colour change in the foot and swelling of the veins on dependency as their chief evidence of an oncoming " vasomotor storm " or of vasodilatation, at once threw doubt upon the validity of their conclusion. This conclusion became still more doubtful when it was apparent that there had been general contentment with the repeated assumption that if during " an attack " the limb is found hot, or is found hotter than between attacks, then this attack comprises an abnormal disturbance of vasomotor nerves. There seemed to have been no attempt to understand how the pain arises, or its relation to a supposed vasomotor disturbance. It is of pain, of course, that a patient mainly thinks when he discusses his attacks. In parenthesis, we here see again a fault that was noticed in the case of auricular fibrillation. A hypothesis was put forward to explain one conspicuous manifestation and this only, to explain redness but not to explain pain ; but no theory can be regarded as satisfactory which fails to explain all manifestations.

I was led by dissatisfaction with current theory, and with the manner in which certain phenomena were explained, to seek cases displaying these phenomena and to make fresh enquiries.

## INVESTIGATION OF A PATIENT.

In giving an account of this investigation in its natural sequence we come next to a clinical case. A young woman

complained of burning pain in her feet, after walking a mile or two. It is unnecessary to relate details, which are available elsewhere. The feet were normally formed and the arteries to them pulsated normally. The dorsal surfaces of the feet presented increased coloration and tenderness, and this colour deepened when the feet were allowed to hang down. When examined the feet were cold ; a thermal junction at the base of the left toes showed a temperature of about 22°, at a room temperature of 18°. Acting on the general principle that a symptom under investigation should be provoked in the presence of the investigator, the patient was asked to walk up and down a room at a pace sufficient to bring on an "attack" of her ordinary pain. After walking for nearly an hour she began to complain of burning pain in her feet. Meanwhile the temperature of the left toes had quite gradually risen to 29·5°. She continued to walk, the pain increased, and the temperature meanwhile rose another degree. Resting with her feet raised gave her relief, the pain gradually passing away and her feet cooling.

It was possible to interpret this observation, as many similar observations had been interpreted in the past, as a vasomotor storm induced in the feet by walking. It would have been more rational to do so if it were known that a normal subject starting to walk with feet cold and continuing, would not acquire similar warmth of the lower extremities. In actual fact it is normal to do so ; and so there was here no evidence of anything beyond a physiological reaction. How could we account for the pain which accompanied the heat ? An obvious enquiry was to ask the same patient, when her feet were again cool, to immerse her foot in water at 31° or 32° ; this resulted in pain, starting within a few seconds in those areas of the foot in which she was accustomed to feel it and of precisely the usual burning quality. Warming these feet to such temperatures was found always to provoke pain, and to higher temperatures severe pain, and this result was independent of the manner in which warmth was induced, that is to say whether heat was conveyed to the foot from without or by its own blood supply. These simple observations at once gave a clue to the origin of the pain ; they indicated clearly that the relation between increased temperature of the skin and pain was the simple one that warmth directly

provoked pain; they further suggested that the malady consisted of a local abnormality of the skin, a suggestion decisively confirmed by finding that the tender areas were those particularly susceptible to heat.

But the case, like most clinical cases, was not uncomplicated, and could not be regarded entirely from the standpoint of a local lesion. For this reason and for others explained in dealing with intermittent claudication, it seemed desirable, if possible, to induce in normal subjects a condition of skin presenting comparable phenomena. This proved an easier matter than had been anticipated and led to the following studies.

### PRODUCTION OF THE "SUSCEPTIBLE STATE" IN NORMAL SKIN.

It was within our experience that skin well exposed to ultraviolet light becomes reddened within a few hours, that the depth of colour is increased by dependency, and that next day the skin is tender. Consequently ultraviolet light was used, and it was soon discovered that skin of the foot or of the forearm so inflamed is sensitive to warmth just in the same way as had been found in the reddened skin of the patient. When such skin is passed from water at 27° gradually to 32° or 34°, pain is provoked, and when plunged into water at 38° to 40° pain, which is at first severe, appears.

Attention naturally turned to other simple agencies known to cause inflammatory changes in the skin; mustard oil was placed on the skin, or the skin was abraded, or frozen, or actually burnt with heat. It was found that, nicely graded, all these methods produced a similar condition of tender redness in the skin, in which burning pain, always of exactly the same kind, occurred from time to time without interference, and always when exposed to warmth. It was familiar knowledge that after burning a finger with heat, the finger becomes continuously painful, and that this pain is increased by warmth and can be abolished by cooling; it had now to be recognised that this phenomenon is not peculiar to heat but is a common after-effect of many forms of injury. The knowledge that heat causes burning pain when applied to the skin, and that this pain continues subsequently in much the same form, gives rise to the idea that the after-effect of heat is continued in a fashion

peculiar to the stimulus. This idea is fanciful and certainly erroneous. Investigation showed that there are differences in the behaviour of the pain following different agencies and injuries of different grades; but that these are differences of degree and not of kind. When the skin is burnt by heat, there is often an appreciable interval of seconds before the burning pain occurs as an after-effect; in the case of slight abrasions this interval is one of 15 or more minutes; in the case of mild freezing and of ultraviolet light it is usually an interval of hours. The appearance of tender redness of the skin, with which the onset of burning pain closely associates itself, is delayed by corresponding intervals. Heat injury was found to differ from the others, and probably for the reason of its exceptional severity, in that pain is provoked in it at an exceptionally low temperature (about 29°); for this reason it gives rise more often to "spontaneous" pain. It soon became clear that in all these instances the skin enters essentially the same "susceptible state," the term by which this common state was now called; this susceptible state may be regarded as comprised in a particular state of inflammation, and, as will be seen presently, includes a special mechanism predisposing to burning pain.

### PROVOCATION OF PAIN IN PATIENT AND NORMAL SUBJECT.

The investigation had now been brought to the stage in which, in all probability, the tender redness of the patient's skin, and that induced in normal skin by various injuries, could safely be regarded as fundamentally alike. A number of other patients showing many or all of the symptoms and signs usually regarded as justifying a diagnosis of erythromelalgia were investigated and further work was done on normal skin. Nothing could be found to upset the idea just expressed of the fundamental similarity of the patients' and of the artificially induced lesions, but much additional evidence was soon gathered in support of it. Thus it was found in all instances that pain could be elicited not only by heat but by unusual cold. It was also found that it could be elicited by rubbing the skin; alternatively it could be elicited by placing the skin on the stretch, the factor probably actually involved in rubbing. The

pain comes and goes with the imposition and relief of tension. This observation threw light upon the pain induced in an affected foot by hanging it down. The phenomenon of pain developing with dependency, also common to patients' and artificial lesions, was shown to be due to the stretching of sensitive structures in the affected skin as the vessels become tense under increased hydrostatic pressures. Similar pain could be produced by throwing a suitable distending pressure onto the main veins by means of a pneumatic cuff (at 70 mm. Hg), the leg being horizontal; and when present it could be relieved at once by throwing a similar pneumatic counter-pressure upon the skin where the pain was felt; such counter-pressure locally opposed the distending pressure within the vessels.

Both in the case of friction and of stretching, it was found that if the stimulus was a powerful one, an after-effect followed. The initial pain subsided and, after an interval of quiescence, it began again, and grew in intensity to last for several minutes; this phenomenon, likewise common to the patients' lesions and to artificial lesions, is remarkable and has, as will presently be seen, a special significance.

## UNDERLYING CAUSE OF TENDERNESS AND BURNING PAIN.

The enquiry into the cause of the burning pain was facilitated by noticing that when a sharply defined area of skin has been made red and tender by ultraviolet light, the tenderness is not confined to the area exposed, but spreads beyond it, especially up the limb, and sometimes distinctly up the veins (Fig. 44). This bordering tenderness could not be attributed to any form of direct action of ultraviolet light upon the corresponding tissues, since these had escaped exposure; and so the idea arose that the tenderness results from some substance formed or released in the exposed area, and diffusing into and similarly affecting neighbouring areas. And since there is a quite obvious association between tenderness and the proclivity to pain in susceptible skin, the further idea arose that this proclivity might also prove to be dependent upon the action of the substance on the nerve endings, rendering them more susceptible to certain forms of stimulation.

Now it has been stated that when susceptible skin is rubbed hard, pain comes during the rubbing and quickly subsides to reappear gradually and to last for a considerable period. The first and second pains are felt by the subject to be alike, but they do not arise in the same way. Presumably the first pain is the direct result of such a stimulus as stretching upon nerve endings already hypersensitive; the return of pain after the stimulus has ceased, its gradual increase in intensity, its persistence, form the first evidence that the rubbing brings into the tissue spaces a substance, which acts on the nerve endings sufficiently

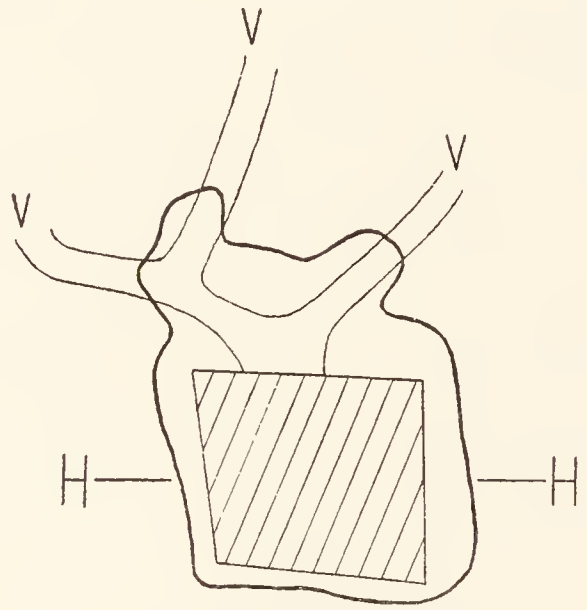


FIG. 44.—(2/3 nat. size). An ultraviolet burn was put down over the area shaded (2·5 × 2·5 cm.) two days previously. The diagram shows the extension of the area of hyperalgesia (H.) beyond this, and its relation to veins (V.), which are coursing up the dorsum of the foot, towards the leg.

to cause them to discharge pain impulses under ordinary conditions of temperature, etc. This idea was now put to the decisive test that has been described in other connections, namely, the test of circulatory arrest. A susceptible area of skin upon a limb was rubbed in such a way that the resultant pain followed in regular fashion in successive tests; the tests were then done with the circulation to the limb free or arrested, alternately. The result was as had been anticipated; the intensity and duration of the first pain was unaffected; but the second pain was indefinitely prolonged and was increased in intensity by keeping the arteries supplying the limb occluded. These phenomena were witnessed both in normal subjects, in whom areas of skin had been injured in various ways, and in the tender red skin of selected patients.

ERYTHRALGIA; THE LOCAL MALADY AND ITS SYMPTOMS.

Omitting further reference to the ultimate mechanism underlying pain, the following conclusions relevant to subsequent argument had now been reached. The skin when damaged by a variety of agencies may be brought into a state of redness and tenderness in which it responds to tension and to temperature with unusual readiness, and the result is in each case burning pain. The pain induced at the time of stimulation by tension is transient, but, when tension has been sufficient, it may be followed after an interval by a slowly developing pain of much longer duration. This state is termed the "susceptible state of skin" or may be more briefly termed "erythralgia." An exactly similar state of the skin occurs as a chronic condition in patients and is responsible for a train of symptoms, which is characteristic. It is a local malady and very probably results from almost any chronic and superficial inflammatory process. It occurs more often in the feet than in the hands. The reddened skin is ordinarily tender. Burning pain is induced in it whenever it is brought up to certain temperatures (about 32° to 34°) natural to the healthy skin, and severer pain occurs transiently when the feet are plunged into warmer water (40°). Quick changes of weather from cold to warm bring more, and from warm to cold less, pain. The patients cannot tolerate many bedclothes, or hot bottles to the feet, for warmth of the body causes a natural and general vasodilatation and the bottle heats the feet directly. So the bedclothes used are light and affected feet are often kept outside them. Walking, by causing natural vasodilatation in feet that are usually cold—for coldness of the extremities is common in such patients and is perhaps largely responsible for the skin becoming damaged—and aided by friction, provokes pain that may quickly become intolerable. In severe cases, or in mild cases suitably circumstanced, the act of hanging a limb down—an act that passively engorges the feet and increases tension in the sensitive skin—is enough to provoke the same kind of pain.

Considering finally the question of vasodilatation, evidence that this occurs as an abnormal event, an integral part of what is called an attack, has never been brought clearly. The idea has had a twofold basis. First it was thought that reddening

of skin such as occurs when a limb hangs down is due to an increased flow of blood through it. Secondly, during "attacks" the limb was frequently found warmer than between them; the simple reason for this, as has been seen, is that pain is induced whenever the skin, which is usually cold, becomes normally warm; the rise of temperature, which precedes the pain, may be due to any cause; it is pain which really constitutes the attack and brings the limb in a state of warmth to examination. Appropriate observations upon patients failed to discover that any rise of temperature follows as a consequence of hanging a limb down, though the limb reddens and often becomes painful in these circumstances.

## COMMENT.

We began by discussing a condition termed "erythromelalgia," commonly regarded as a rare disease, thought primarily to involve the vasomotor system, and identified by a general statement of symptomatology. Our enquiry, resulting originally from dissatisfaction with the recorded evidence for vasomotor disturbances, has brought us to a conception of wider significance; and to define a common condition of the skin, presumably always marking a certain phase or form of local inflammation, recognisable by a group of symptoms now interpreted upon a common basis. Our original enquiry has led us away from the attempt to identify a single disease, and has brought us to recognise a state of the tissues common to a large number of distinct maladies. It is to be recognised that no phenomenon has been established as occurring in relation to what has been called "erythromelalgia" in the past, which is inconsistent with the present description and interpretation, but almost all past description may be brought into active support. Interest can no longer concentrate satisfactorily in an attempt to define a disease "erythromelalgia"; the work there is to do lies in endeavouring further to understand the underlying factors of a state which, to link it with past tradition, has been described and named "erythralgia."

From the history of the word "erythromelalgia" there are, however, lessons to be learnt. One function of clinical science is the isolation, description and naming of maladies, the "discovery of new disease" as it is sometimes expressed. Its

value to investigation has been noticed on page 19, in dealing with cardiac irregularities. But this function can be over-exercised. If new descriptions are sought too eagerly, and especially if separation is based exclusively upon loose groupings of symptoms, without reaching a pathogenetic or mechanistic basis, or without attempt at close definition, conditions essentially distinct are apt to be confused and further errors become inevitable. A new term, employed and accepted, may bring with it a sense of precision where little or none exists ; and it may inculcate a feeling of finality, before serious investigation has really begun ; these tendencies discourage research when and in so far as they conceal how little is actually known. For 60 years the term "erythromelalgia" with all that it then connoted has stood almost if not quite unchanged ; it has acted as an anæsthetic rendering medicine unresponsive to the idea that there is no such special malady, and incurious of the meaning of a number of phenomena often to be observed in patients ; phenomena which at once yield up much of their meaning when probed by simple and commonplace enquiry conducted in an atmosphere free from the prejudice of nomenclature. Any who critically read the records of this subject can scarcely fail to perceive the undue stress, which has continued throughout these 60 years to be laid on the original articles of a physician, holding a great repute as diagnostician and teacher, and upon the unfortunate title of "vasomotor neurosis," which he chose ; there is to be obtained from this reading unmistakable warning against the voices of authority and tradition.

Disorder of vasoconstrictor and vasodilator nerves as a hypothesis to explain disease has provided an unfailing fascination for the physician almost from the date of their discovery. The first investigations of these nerves were published in 1852 and between 1855 and 1858 their functions, thanks chiefly to the work and teaching of Claude Bernard, were beginning to be known to the world. In 1862, Raynaud seized upon this new physiology to explain attacks of white fingers, and not many years later Mitchell was explaining redness of the skin on a nervous basis. It is an interesting sequence of dates and of ideas, in itself now seen to display an important lesson. When a new and impressive physiological discovery is made, it does

not follow that the time is ripe, or nearly ripe, for its application to the theory or practice of medicine ; and such application is not merely a matter of introducing the new idea where it seems most appropriately to fit. A proper application is often as difficult, and may be more difficult, to accomplish than the original discovery, which prompts it ; it requires further and close study, often a deliberate extension of physiological knowledge, almost always new clinical investigation. The understanding of symptoms does not come merely from the application of physiological ideas ; it has its own appropriate basis of observation and experiment. Hasty application is as likely to impede as it is to promote progress. Application should be a deliberate and reasoned act and is one of the many, though it is not the most important, functions of clinical science.

NOTE.—Those interested in the detail of these investigations, and requiring the case notes of patients, will find them in "*Clinical Science*," 1933, 1, *p*. 39 and 175 ; in these articles, too, will be found the references to the chief relevant papers.

# CHAPTER 15.

## DIAGNOSIS.

It has been indicated in the opening chapter of this book that the object of discriminating accurately between different diseases, is that the power to identify them, as in the case of biological species, allows them to be separately and more thoroughly studied; it permits the collection of precise information relating to the cause, mechanism, natural history, and management of disease. To ensure a high degree of accuracy in this discrimination is in time vital to all branches of work undertaken upon patients; it is therefore one of the goals of clinical science; and it requires the use of every useful method available for studying disease. There is another, related, but less accurate type of work, namely, the identification during life of individual instances of disease already discriminated; this is diagnosis. The art of diagnosis would be perfect if it allowed invariable recognition of all named diseases; but it fails to reach this pitch of efficiency because of its need to accomplish recognition quickly; applying as it does to the individual, from the circumstances in which it is undertaken, diagnosis can gather only a little advantage from time and none from death; its method differs in this and in other ways from that which attempts to discriminate between diseases. Nevertheless the two branches of work hold much in common, because discrimination also depends very largely upon events witnessed in the living and because, in the building up of diagnostic method, what is found during life is often closely compared with what can be discovered after death. Therefore, investigational work upon diagnosis and upon discrimination of disease can often proceed simultaneously and upon similar lines.

The improvement of diagnostic methods is not only a practical aim of clinical science but it affects this science directly. When an investigator is dealing with a clinical problem, the patients upon whom he works are necessarily all chosen upon a diagnostic basis. But to conserve investigational effort, it is necessary to choose material for study in which diagnostic error is small; and to keep the work sound, it is essential either to choose material in which diagnosis is without error, or to render the identification secure ultimately by following the disease to its termination and the subject to autopsy. In the case of non-lethal maladies we depend entirely upon diagnosis, and the soundness of our work is proportioned to the accuracy of diagnosis; investigation based on diagnosis that is not free from error has but fugitive value and is wasteful. A lesson to be well learnt from this point of view is that it repays to spend more time than is usually given in the preliminary selection of cases to be investigated.

Since complete security of diagnosis must be the aim of every investigator of disease, it becomes a matter for his close consideration and study. If we place on one side instances of disease in which the morbid tissue is visible, can be made visible, or is palpable—diseases often recognisable as soon as seen or felt—there remain two methods of identifying a patient's malady. One is empirical, and the other rational. In the first, a familiar group of associated symptoms and "signs" the significance of few or none of which is understood, is recognised and is interpreted as indicating the presence of a given malady. In the second, consideration of one of more phenomena, the mechanism of which is known, points with certainty to the site or character of the disease, and shortly leads to the discovery of its nature. The empirical is giving place to the rational method, and ultimately will be replaced by it. This change is happening as the meaning of symptoms and "signs" becomes clear, a fact emphasising the importance of the relevant investigations. The transformation is happening gradually, and the short steps of its inevitable progress are often little heeded and too lightly appraised. The empirical method is the primitive method and is inevitable when study begins, but reliance upon it is a not infrequent source of fallacy in investigation. There would be less chance of error if symptoms and signs formed themselves

into quite simple, constant, and distinctive groups, but this they do not do. There is a company, but it varies ; sometimes there is a stranger, sometimes an absentee ; recognition of the company is made to depend upon a nucleus, the numbers and constitution of which are not precisely specified. What is here said of diagnosis, is also often applicable to the discrimination of diseases. The most frequent fallacies, to which the identification of disease from grouped phenomena leads, result from symptoms and signs coming to form the basis of definitions; they have been illustrated especially in Chapter 14. These definitions lack precision, lack security, cause confusion in thought itself and in its transference. Thus to the investigator the use of the empirical method in the discrimination of disease, and in the recognition of disease in individuals, is rightly regarded as a matter of temporary expediency, and conclusions based upon its use are viewed with appropriate reserve and are not accepted as solid foundation from which further work and conclusion can proceed.

From the standpoint of rational diagnosis there is a very high value in work that properly elucidates the meaning both of subjective and objective phenomena. Methods of studying symptoms, and the mechanism of their production, have been illustrated freely in this book. The studies of axon reflexes, in Chapter 9 have been introduced to illustrate the manner in which two tests belonging essentially to the rational system of diagnosis came to be devised and rendered reliable. It is not to be inferred that signs of just this kind are the only ones of value in diagnosis ; but these usefully illustrate, and lead to fuller realisation of the differences between the empirical and rational method of work. Symptoms and "signs"—or as we may alternatively and significantly call them "portents"—under a purely empirical method are no more than phenomena associated with named diseases, supposed or real. Symptoms and other phenomena under the rational system are used to locate the disease, to measure its extent, and to ascertain its nature and mechanism. Failure of an axon reflex, such as has been described in Chapter 9, will not indicate the presence of a given disease ; it tells of the condition of a certain kind of cutaneous nerve, and thus brings an immediate clue to the sort of structure involved by the disease and to the site of the disease.

The phenomenon "capillary pulsation" of Chapter 6 is not regarded to-day as a "sign" of aortic regurgitation, but as an evidence of the state of the superficial arterioles, being mainly used to identify a certain measure of vasodilatation. Spontaneous vasodilatation is part of the picture in several diseases in which capillary pulsation, rationally used, aids identification. Occurring spontaneously or provoked deliberately it enables us to declare the small arteries and arterioles free from obstructive structural disease. These are simple illustrations of the general trend of diagnosis to become rationalised. But the diagnosis of very many diseases still rests in greater or lesser degree upon the empirical basis; to eliminate what remains of the empirical by seeking the inner meanings of symptoms and signs is a great work which clinical science has still before it.

# CHAPTER 16.

## PROGNOSIS.

Rational prognosis is, and will remain, empirical in its method of arriving at conclusions. To base prophecy upon considerations other than those of experience is sometimes necessary as a temporary expedient, but theory should never be permitted to weigh against actual experience. Investigation leading to sound prognosis consists first of accurate diagnosis and next of studying the after-histories of numerous patients. Many simple diseases are known to run a brief course to recovery, a few are known to be brief and invariably fatal despite treatment. The outcome of such diseases as chickenpox and acute bacterial endocarditis require little or no further investigation; information relating to the natural history of such diseases has been easy to obtain and is soon possessed by all who have to manage them.

There is much more difficulty in gathering accurate information concerning chronic disease, and especially concerning maladies that are complex and that run very variable courses. These here require closer consideration. Prognosis will always possess elements of uncertainty, owing to the occurrence of occasional and disastrous events that cannot be foreseen and timed. It is beyond question, however, that our knowledge of and power to predict the usual course taken by very many chronic maladies, and of some acute ones, and the influence of these maladies upon the duration of life, leaves much to be desired and much that might be remedied. Current statements have been based too largely upon general impressions of personal experiences, tinged sometimes by theoretical notions of how this or that factor is calculated to affect life-history, biassed at others by dread of what is not understood. A phenomenon unfamiliar to the observer, is very apt to be regarded instinctively as one

of ill omen. The same instinctive element probably in part accounts for the notoriously, but unwarrantably, gloomy view that is taken of many newly described diseases ; here, however, pessimism results largely from mild cases being at first overlooked and of severe cases at all times attracting exceptional attention. It is obvious that in many directions there has been little thorough study ; there are in fact very few collected and published records of the life histories of groups of unselected patients, such as could alone form an adequate basis for conclusion.

If disease is very variable both in manner and rate of development, it is obvious that a simple statement relating to prospect cannot possibly suffice ; and that an attempt must be made to ascertain the most significant features of the disease, so that the cases may be subdivided into corresponding and satisfactory prognostic groups. Out of a large number of such features one or more that will prove of outstanding value may become selected. Such must be sought diligently and critically ; otherwise the assignment of prognostic values to given phenomena may readily go astray. If, for example, we set out to ascertain the prognostic significance of the systolic apical murmur and enquire what is the life history of patients who exhibit it, we may very easily be led to an erroneous answer, as past experience has actually shown. Go into the street and collect the first fifty people presenting this sign and the first fifty who fail to display it, and compare the after-histories of the two groups. Experience shows that in the group of those displaying the murmur the sickness and death rate will be the higher. It may be difficult to resist this experience from influencing our view of the significance of the murmur in question ; yet it is irrational to allow it to do so, as a little thought will show. For the fifty without murmur will be for the most part healthy, whereas among the fifty displaying murmur there will be some with histories of rheumatic fever, with enlarged hearts, and lesions such as aortic disease or mitral stenosis. Obviously the difference between the prospect in the two groups may be due entirely to such associated factors and not in the least to something underlying the murmur under discussion. It is essential, if the significance of the murmur is to be ascertained, that in the comparison the second group should

form a proper control to the first, and that the two series of subjects should be alike in every respect apart from the murmur. The test is valid if a group of cases presenting systolic apical murmurs, and no other abnormality of any kind, is compared with a group of normal subjects of similar age ; it is also valid if the subjects of both groups equally display breathlessness, enlargement of the heart, aortic lesions and other defects. In either of these instances the control is adequate. But when such controls have been used it has soon become clear, that the systolic murmur has insignificant value in assessing the gravity of chronic cardiovascular disease. The employment of wholly adequate controls is vital in this matter of judging prognostic values, but neglect of this underlying principle has been widespread. Very few single manifestations of complex disease that have been judged to possess prognostic significance have yet passed the test of rigid control, and it is largely for this reason that prognosis in these types of malady has remained crude and unreliable. If some phenomenon is repeatedly found in patients known from other evidence to be gravely ill or actually moribund, inclination to judge the phenomenon itself to be of ill omen must be resisted. It may form one of an association, which as a whole is ominous, and there is no harm in the fact being recognised ; but when, merely because of the association, the same significance is attached to the phenomenon standing by itself, the doorway to fallacy has been thrown widely open. A doorway of the same kind is opened when, as not infrequently happens, the value of a new diagnostic sign is similarly proclaimed upon a basis of association with other diagnostic signs. It has been shown that in exploring a given manifestation of disease it is essential to divorce its significance from that of associated manifestations ; the divorcement will not always be easy to accomplish ; it may involve a long and arduous task in collecting suitable material and following it, and critical judgment in ultimately arranging it ; and we may be forced to the expedient of treating these problems statistically. A unique example of such work has recently been completed by Grant* in the field of chronic heart disease, and has for its basis the after histories of 1,000 cases followed for 10 years in my out-patient department. The investigation covers too wide a field to be reviewed here, but the

* *Heart, Vol.* XVI, *p.* 275.

analytical method used may be illustrated. Having shown by similar methods that a subdivision of cases into forms of valvular disease provides no satisfactory basis for prognosis, even when these types are again subdivided etiologically, Grant ultimately

| Circulatory Efficiency | Cardiac enlargement | | | | |
|---|---|---|---|---|---|
| | None | Slight | Moderate | Great | Totals |
| Exercise tolerance Good | 1/9 (11%) | 5/17 (29%) | 2/8 (25%) | — — | 8/34 (19%) |
| Fair | 13/64 (20%) | 23/96 (24%) | 33/84 (39%) | 0/2 — | 69/246 (28%) |
| Poor | 10/48 (21%) | 103/221 (47%) | 143/285 (50%) | 72/95 (76%) | 328/649 (51%) |
| Congestion | 1/1 — | 5/6 (83%) | 33/34 (97%) | 29/30 (97%) | 68/71 (96%) |
| Totals | 25/122 (20%) | 136/340 (40%) | 211/411 (51%) | 101/127 (80%) | 473/1000 (47%) |

presents in the accompanying table two chief factors, which are found to count in chronic heart disease, namely, circulatory efficiency and the heart's size. In the table the deaths occurring within the ten-year period are correlated with circulatory efficiency, as judged by the exercise tolerance or by presence or absence of congestion, and with cardiac enlargement. In each rectangle of the table is a fraction ; the denominator gives the number of cases, the numerator gives the deaths in the ten-year period ; in brackets the percentage values of the fractions are seen. Now exercise tolerance and heart size can be shown to be related in the sense that in general the larger the heart the worse the exercise tolerance ; this table allows the general prognostic statement to be made that the larger the heart and the less the tolerance of exercise the worse the outlook. Taking into account these two factors only, the 1,000 cases become divisible into groups through which the prognosis proceeds by steps from good to bad. Thus, considering enlargement alone, the death rate rises in those without signs from 20%, and it increases with increasing heart size through 40% to 51% to reach 80%, when the heart is greatly enlarged. Again, considering circulatory efficiency alone, the death rate in those with good exercise

tolerance is but 19%, and rises to 96% in those whose tolerance of exercise is reduced to nothing and congestion is present. Moreover, even within the same grade of enlargement or of exercise tolerance, tolerance or enlargement respectively serve further to differentiate the cases. These factors, therefore, are significant. But it has to be pointed out that this statistical method has more value in eliminating false ideas than in providing us with an exact basis for individual prognosis ; for, in the measure in which it is based on probability, prognosis in practice remains conjectural.

Investigational work upon prognosis requires that given types of patient, and in adequate numbers, should be under supervision for periods of many years. It is work that can rarely be undertaken satisfactorily in hospitals. Patients attending hospital cannot safely be regarded as representative ; in many instances the severer types of the disease are over-represented, a statement that applies especially to patients dealt with by the senior staff of such institutions. The most important reason, however, is the inevitable loss of contact with a large percentage of the cases diagnosed. It is insufficient that a reasonable number of cases of a given disease should be followed, it is by no means immaterial that contact with many is lost. For on the one hand there is the particular tendency for quickly fatal cases to be filtered out and recorded, on the other hand cases refractory to treatment are prone to drift elsewhere, and many patients who recover completely fail to give information of the fact. Hospitals are usually in large centres and serve shifting populations. The requisites to investigation are that the group of cases chosen for after-history work should be subject to as little uncontrolled selection as possible, and that the original group should be followed for the necessary period of time with little or no diminution of its numbers. Unless the cases successfully followed reach a very high percentage, it becomes necessary positively to demonstrate that those with whom contact is lost are not those running unusually favourable or unfavourable courses. Thus after-history work requires particularly advantageous conditions for its prosecution. It can be carried out most successfully in small communities, where the population is relatively stationary, or where contact between patients and medical man is ensured over long periods by pension or life assurance.

# CHAPTER 17.

# THERAPEUTICS.

## DISCOVERY OF NEW REMEDIES.

No one can be engaged long in the investigation of disease in human beings without considering the discovery of remedies, remedies that will cure disease, alleviate disease, or relieve its symptom. In discussing how to proceed most advantageously to this end point of discovering remedies, it will be helpful to consider the way in which remedies have been found in the past; and it will simplify matters if consideration is confined to instances in which the value of the remedy is universally acknowledged. New remedies have been discovered in one of two ways, either by a process of reasoning, or by accident. Manifestly, surgical treatment has developed almost wholly upon rational lines, as exemplified by its repair of wounds, its replacement of displaced structures, its removal of foreign substance or of diseased tissue. When we turn to medical therapy, numbers of potent remedies can be named, and these may be placed in two interesting groups. There are, on the one hand, remedies that have likewise arisen by a process of reasoning, the administration of food for starvation, of salt for the cramps of over-sweating, of thyroid for cretinism, of suprarenal cortex for Addison's disease, of insulin for diabetes, the use of antitoxin for diphtheria and tetanus, and the removal of thread worms by simple enemata; and it will be found that this group consists almost exclusively of remedies making good deficiencies of food stuffs, or of substances elaborated by the body in its everyday processes or in its defence against invasion, or of the simple removal of injurious agencies. There are, on the other hand, remedies that have originated in accidental observations, the administration of mercury for syphilis, of iron for chlorosis, of

foxglove for dropsy, of quinine for malaria, and of opium for pain. From their nature, it is almost inconceivable that knowledge of such remedies could have originated differently; they are drugs, substances for the most part foreign to a normally acting body, and *a priori* reasoning could not have predicted their actions. This simplified grouping of remedies is instructive. It teaches that it would be foolish to set out in the expectation of discovering remedies of the second group. And it teaches that a remedy of the first group will be found only by knowing intimately the processes of the body and its reactions to environment. It would not alter the argument in its breadth if the list of maladies and appropriate remedies were fuller; the fact remains that direct search for really new medical remedies is an unprofitable branch of study; and that the search must be indirect and through investigations of the cause and mechanism of disease and its symptoms; for sooner or later knowledge of these matters will suggest methods of treatment.

Deliberate research in therapeutics takes for the most part a different course. The two groups of remedies alluded to are not comprehensive. Between them is a group of many which originated more or less accidentally, but which close investigation has rationalised, perfected, or actually diverted to some new purpose. The use of emetin for amœbic dysentery, of quinidine to stop auricular fibrillation, of massive doses of iron for microcytic anæmias, of digoxin for the control of auricular fibrillation, of vitamins for deficiency diseases, and of various hypnotic or anæsthetic substances, are among many examples, the last named especially illustrating the need for close linkage with pharmacology. Clinical science in its relation to new treatment would seem, therefore, to have the following outlook. Surgical technique will continue its rational development, though this will still be moulded by experience as it proceeds. In other fields clinical science may discover completely new remedies for disease, but will do so by developing a greater understanding of disease and of the reactions of the body. Clinical science must remain alert to take advantage of new accidental discoveries; it must be conversant with contemporary physiological and pharmacological progress, from both of which the first suggestion of a valuable remedy or a modification of an old remedy comes from time to time. But in its linkage with pharmacology it

must recognise that, in so far as both manner and intensity are concerned, the action of a drug on man is not necessarily the same as the action on an animal, and that the action on the diseased is not necessarily the same as on the healthy man. It has much work to do in giving proper sanction to old remedies, in perfecting these, and in testing selected or pure substances derived from the crude vegetable extracts now in use. It is not through easy, but often fallacious, general impressions that full progress is to be expected, but mainly through deliberate, unbiassed, and controlled study of the reactions of patients to given remedies.

## TESTING THE CURATIVE PROPERTIES OF REMEDIES.

*Cure of disease.* Apart from those diseases of which the cause can be recognised and eradicated, for example, when the further action of an injurious external agency can be stopped, when operation can successively remove a growth, or when a parasitic organism in the body can be destroyed, cure of disease in the full sense is hardly known. In dealing with a chronic disease, real cures are usually unmistakable, owing to the long preliminary period which elapses with little change, and the quick restoration to health following the administration of the remedy. It is more difficult to judge the result in the case of acute disease, because in this a change will soon come whether the remedy is given or not, but when it will come, and what the kind and extent of change will be, are not known precisely. Most patients who are acutely ill become well without our interference; and the fallacy of confusing recovery with cure because it follows a remedy is obvious and well recognised. Because acute illnesses usually behave in this way, it should be evident that if in one instance a patient recovers after the use of a remedy and another dies in similar circumstances, there is more reason to conclude that the latter instance rather than the former is an example of cause and effect. But the universal reluctance even to contemplate the more likely conclusion shows that judgment is biassed and emphasises the value of control observations. To ascertain in general if a remedy succeeds or fails, and the measure of its success or failure, two groups of acute cases should be selected, being composed as similarly as

possible ; the patients of the groups are then treated in exactly the same way and simultaneously, except that in one group they receive the remedy and in the other, they do not. The latter or control group serves to determine the natural course of the malady tested at the time and under simple basal conditions. These are the conditions required by the experimental method, and the result is judged by the death rate in the two series, or in the case of a non-lethal malady, by the speed of recovery. In practice such experiments can rarely be carried to a fully satisfactory conclusion in the case of a serious malady, for the ethical reason that the moment the remedy is strongly suspected to be successful, it may not be withheld from the control cases. Comparison between treatment of a series of cases under an earlier regime with later treatment of a second series under a new regime is even less satisfactory, owing to variation in the severity of different forms of sickness from time to time, and the greater difficulty of ensuring constancy in the basal conditions of testing. Naturally, convincing evidence in such experiments is more likely to be obtained if the action of the remedy is a potent one. Actually very few deliberate experiments of the kind described have been carried out even in the case of the less serious maladies ; it is regrettable in so far that the neglect of controls may be said to constitute neglect to ascertain the natural course of the malady. At the same time it is to be recognised that the statistical method of testing treatment is never more than a temporary expedient, and that but little progress can come of it directly ; for in investigating cases collectively, it does not discriminate between cases that benefit and those that do not, and so fails to determine criteria by which we may know beforehand in any given case that treatment will be successful.

*Alleviation of disease.* In ascertaining the values of remedies used to alleviate disease, we deal for the most part with chronic maladies, and usually the testing is not difficult ; thus when insulin is used to govern carbohydrate metabolism in diabetes, or digitalis to influence heart failure in auricular fibrillation, the main result is soon obvious. If we are to judge the effects of the remedy accurately however, casual observations will not suffice. It will be observed that in treating chronic cases, whether we are dealing with cure or alleviation, the patient

himself usually forms the control; we are not often driven to the cumbersome and less satisfactory device of control by treating two groups of patients. In the testing the patient is brought under observation for an adequate control period, its length depending upon the speed with which the remedy takes effect; and during this period his environment is maintained as constant as is necessary to keep his condition uniform and suitable for testing. The first time I saw such tests carried out they were undertaken by James Mackenzie. He put patients suffering from auricular fibrillation to bed under simple conditions of dietary and quietude until for a week or ten days their condition had become constant. The ventricular rate was used as a chief

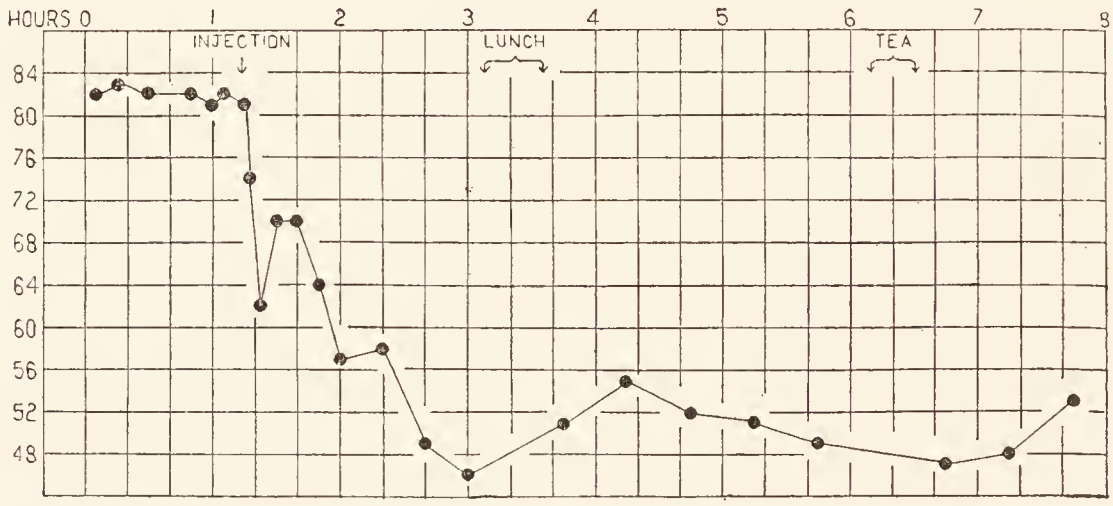


FIG. 45.—(After E. J. Wayne). The effect on the ventricular rate in auricular fibrillation of 0·9 mg. of digoxin given intravenously. A control period lasting a little more than an hour suffices because the drug produces a profound effect within a similar period.

objective guide. It would be running level in a chart composed of frequent readings made instrumentally. Digitalis or other drug was then given in the full doses of those days (1 drachm of tincture a day) and the reaction of the patient to the remedy would be judged both from the ventricular rate and from other manifestations; the reaction to digitalis would begin after about 5 days and would be complete in 8 or 10 days. The long preliminary rest was quite essential, since rest by itself usually resulted in a conspicuous fall of heart rate and betterment of the patient's state. Without the initial control period neither the onset nor the extent of the action of digitalis could be ascertained accurately. In instances in which the remedy acts more speedily,

as do the pure glucosides of digitalis when given intravenously, a shorter control period suffices (Fig. 45). Speaking generally, a control period is essential in providing a correct base line from which to measure an effect, and to ensure that there shall be no confusion between the effect of the remedy tested and similar effects due to associated circumstance. It is remarkable how often in the latter respect precaution is overlooked. It is said of a man that he suffered in his daily work from severe and repeated attacks of angina pectoris ; that he was put to bed in hospital, and sympathetic ganglia excised or nitroglycerine given; and that from that time until he was discharged, weeks or months later, his attacks disappeared. Statements of this kind are valueless as evidence of the potency of the specific remedy employed.

A variation of the method of testing described and one which is often applicable is to administer the remedy repeatedly between appropriate intervals of control, so that the effect of the remedy is seen repeatedly. A regular and uniform response in such circumstances provides the most reliable evidence we can obtain. The investigation of a remedy by the group method is illustrated in the table and remarks on the next page.

*Relief of symptoms* is considered separately from alleviation of disease only because it introduces us to a common source of error, namely, reliance upon patients' statements. Patients frequently state that a symptom is declining when it is not ; this habit results from the hope that they are recovering, from aversion to believing that an operation or course of treatment has been submitted to in vain, and often from the simple but kindly desire to please the doctor. In investigation very great caution is necessary in accepting patients' statements in judging the results of treatment. Whenever possible objective phenomena should be used to replace them and, when this is impossible, devices to render them in part objective should be employed. Thus the stated effect of a remedy upon the symptom breathlessness is to be replaced by observations upon rate and depth of breathing. Statements relating to such a symptom as pain are more difficult to check, though there are recognisable reactions to pain, which can be used as guides from time to time. A subjective symptom may be rendered partly objective by accurately noting the times at which it is said to come and go, and comparing the times in repeated tests and relating them to

| Treatment group | | I | II | III |
|---|---|---|---|---|
| Cases ... ... ... ... ... | | 52 | 75 | 46 |
| Average age ... ... ... ... | | 46·2 | 49·0 | 44·8 |
| Complicated cases ... ... ... | | 14 (27%) | 20 (27%) | 7 (16%) |
| *Aorta*: aneurysm ... ... ... | | 6 (11%) | 8 (11%) | 3 ( 6%) |
| dilatation ... ... ... | | 30 (58%) | 48 (64%) | 21 (46%) |
| no dilatation ... ... | | 16 (31%) | 19 (25%) | 22 (48%) |
| *Exercise tolerance*: | good and fair... | 11 (21%) | 13 (17%) | 5 (11%) |
| | poor ... ... | 37 (71%) | 60 (80%) | 35 (76%) |
| | congestion ... | 4 ( 8%) | 2 ( 3%) | 6 (13%) |
| *Cardiac enlargement*: | little or none | 15 (29%) | 19 (25%) | 11 (24%) |
| | moderate ... | 28 (54%) | 33 (44%) | 20 (43%) |
| | great ... | 9 (17%) | 23 (31%) | 15 (33%) |
| Cases living uneventfully and unchanged ... ... ... ... | | 12 (23%) | 8 (11%) | 7 (15%) |
| Deaths ... ... ... ... | | 25 (48%) | 48 (64%) | 31 (67%) |

Grant's summary of an investigation of treatment in 175 cases of syphilitic aortic disease. The cases were placed in three groups without selection and treated as out-patients, (I) with arsenic in intensive intravenous courses, mercury inunctions and iodides, (II) with iodides only, and (III) without any specific remedy. All but two of the cases were followed for a 10 year period or till death. The purpose of the treatment in Group I was to arrest active disease by destroying the spirochaete, and thus to alleviate the subsequent course of the malady. The table shows the groups be to sufficiently comparable in respect of age and condition at the beginning of the period. The after histories show the death rate to be lowest (48% as compared with 64 or 67%) in the group treated with arsenic.

This table is inserted to illustrate method rather than to compare the relative values of treatment by arsenic and by iodides. A chosen malady running a variable course was being treated and, *a priori*, conspicuous effects were not to be expected ; to ascertain the result of treatment a large scale experiment was required; the less conspicuous the benefits of treatment, the larger the number tested must be. Consider firstly the number of cases here treated and followed, and the period of following ; and secondly the result. It may be that in this instance the result is commensurate with the labour ; but it is clear that if the labour were much greater, and the result a little less definite, it would not be. Yet the method employed of analysing the effects of remedies in this and similar instances is in fact the only sound one at present available ; for it is precisely in such instances of treatment, when effects are relatively inconspicuous, that clinical impressions are valueless.

acts that provoke or remedies that relieve it. To show by example how statements regarding pain may be checked, attention may be recalled to Fig. 37, page 123, which illustrates studies of angina of effort and how nitroglycerine affects these attacks of pain.

### RATIONALISING AND PERFECTING REMEDIES.

What there is further to say on treatment may be conveyed by illustration and comment.

*Quinidine and auricular fibrillation.* A patient, suffering from paroxysmal auricular fibrillation, told Wenckebach that quinine would stop his paroxysms. Wenckebach, having tested quinine on a second case of auricular fibrillation, named this drug as capable of bringing the disorderly action to an end ; and thus prompted Frey to use and compare quinine and allied alkaloids upon cases of chronic auricular fibrillation. Frey found that quinine is much less potent than its isomer quinidine and that, by administering the latter, normal rhythm can frequently be restored. This action of quinidine and the conspicuous therapeutic benefit, which follows in selected cases, are now generally recognised. The discovery of this valuable remedy began when the potentiality of an accidental observation was recognised. There followed a period during which numerous experiments explored the effects of this alkaloid upon man and animal, to determine its pharmacological action, the reason why it brings auricular fibrillation to an end, the best manner of administering it therapeutically, and the most suitable cases upon which to employ it. These problems were attacked simultaneously, and almost exclusively by clinicians, many of whom, while studying the therapeutic effects, became at the same time their own pharmacologists. Thus from the first the work was co-ordinated, and the various problems were quickly solved. There will be no attempt to present this work as a whole or in historic detail, but certain phases of it will be described to illustrate method and the manner in which the study of a remedy may progress.

It was soon found that when quinidine is administered to a case of fibrillation of the auricle in adequate dosage the oscillations of the fibrillating auricle become gradually slower and larger, while paradoxically the ventricular beating quickens (Figs 46 and 47). In cases successfully treated, after the

auricular oscillations have diminished in number from 500 or 400 to 300 or 250 per minute, a sudden change happens ; the auricle ceases to fibrillate and shortly begins to beat regularly and slowly. Its normal mechanism has been restored. The

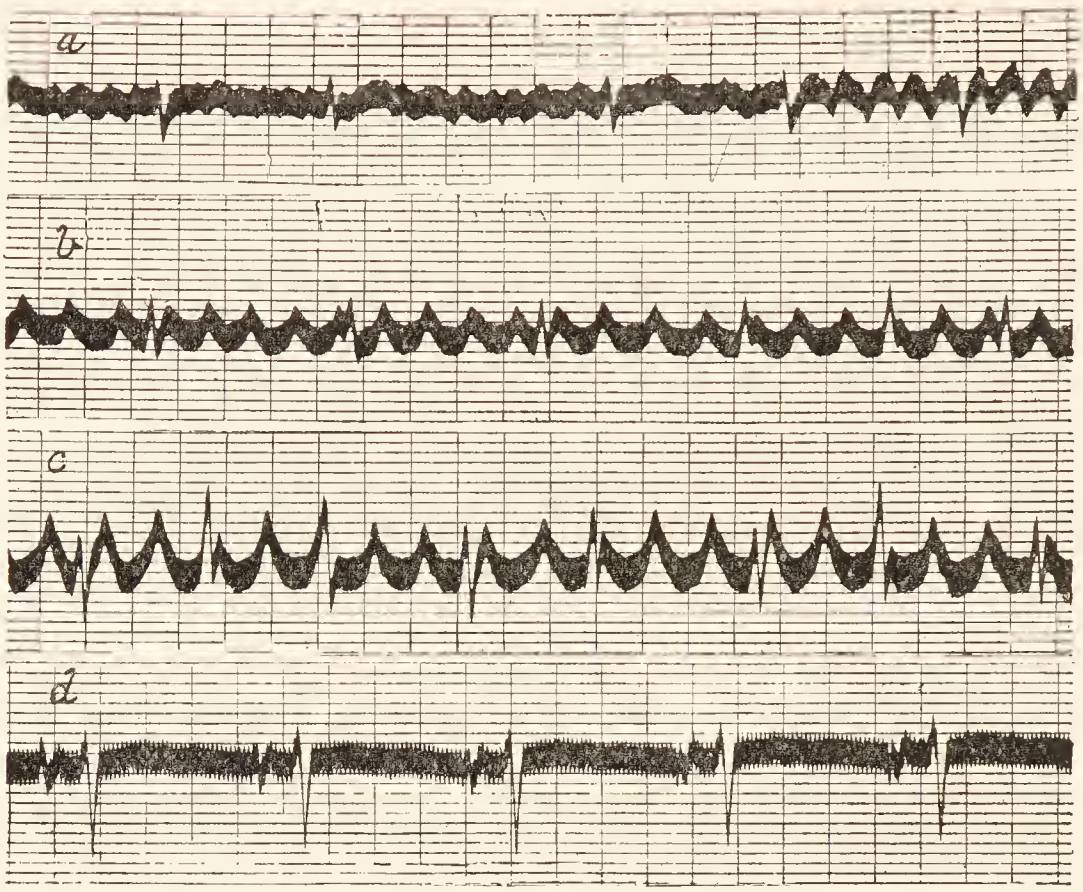


FIG. 46.—Four curves from a pair of contacts arranged over the sternum in a case of auricular fibrillation. Vertical lines represent 1/5 sec. (*a*) Before treatment ; auricular oscillations at a rate of 450 per minute. (*b*) At the end of the first day's treatment, and after 3 doses of quinidine (0·4 gram), the rate has fallen to 296. (*c*) At the end of the second day's treatment, and after 6 doses of quinidine, the rate has fallen to 247 and the oscillations have become almost regular, as in flutter. (*d*) Sixteen hours later and after a final dose (the seventh) of quinidine, the normal rhythm has been resumed. Note the quickening of the ventricular beating displayed in curves *b* and *c*.

effect on the auricle is most clearly displayed in electrocardiograms taken with the electrodes placed on the chest near the auricle ; in such curves the rates of beating are easily estimated. In systematic work the relative potency of different pure alkaloids was ascertained by giving single and equal doses under constant conditions and plotting together the resultant curves of rate (Fig. 47). The order of potency so judged was found to be quinidine, cinchonidine, cinchonine, and quinine. The potencies of quinidine and hydroquinidine, a common contamination, were found to be almost equal. The curves resulting from

the oral administration of salts of different solubilities (sulphate, bisulphate, and bihydrochloride) showed that the alkaloid enters the blood stream at the same rate and in the same total quantity in each case. When the effect of a single dose of quinidine was

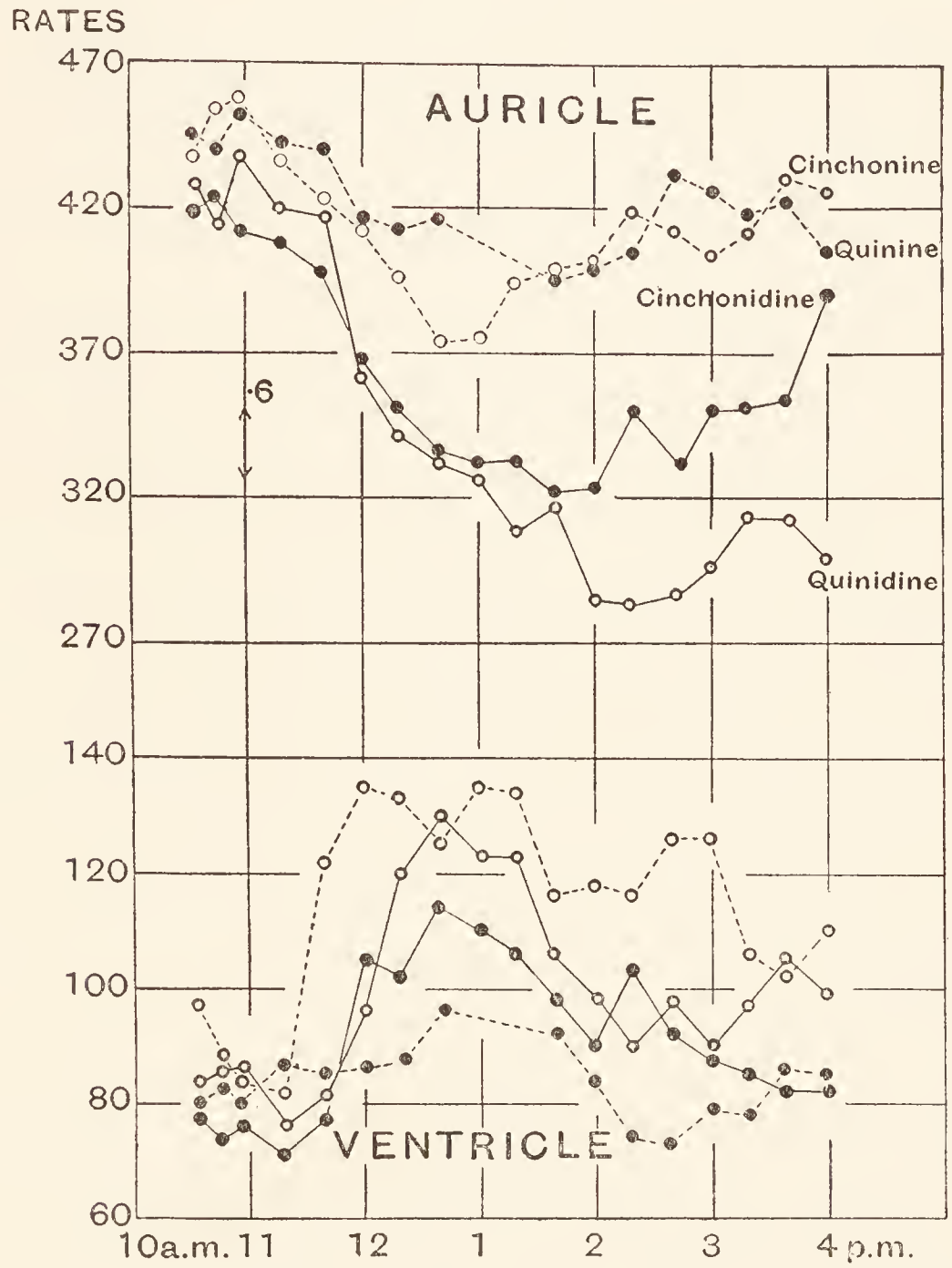


FIG. 47.—A chart comparing the effects on the auricular and ventricular rates of equal test doses of quinidine, cinchonidine, cinchonine and quinine, given in single doses of 0·6 of a gramme on the 8th, 13th, 31st of March, and the 4th of April, respectively. (After Grant and Iliescu).

followed to its end point, the complete curves took the form seen in the diagram (Fig. 48). The alkaloid is rapidly excreted in the urine and, as excretion proceeds, its effect on the heart quickly declines. The optimal effect was found to be reached in about 2 hours, but not to be long maintained. From such curves it seemed

clear that continued or increased reaction requires repeated doses at 4 to 6 hour intervals, without break. Actual trial proved this form of dosage to be necessary in obtaining full effects.

The arduous work of determining the types of cases of auricular fibrillation suitable for quinidine treatment, of following up the patients to ascertain the stability of the restored normal mechanism, will not be described here ; it proceeded simultaneously upon the plan of trial and record of result ; it was carried out by the combined effort of very many workers in different countries and led to the formulation and acceptance of simple guiding rules.

The whole of the work so far described went forward without suggestion or other aid from pharmacology. The pharmacological work concerned itself with the action of quinidine upon the normally beating, and not upon the fibrillating, heart, and it was undertaken from a distinct point of view, namely, to determine the manner of the alkaloid's action, and so to rationalise a form of treatment, the value of which was being proved by purely therapeutic methods.

The effect of quinidine upon the fibrillating auricle has been described as consisting firstly of slowing of its action, and secondly of cessation of abnormal with restoration of natural beating. To ascertain how these changes are brought about, it was necessary to know what influence quinidine exerts upon heart muscle. As information so obtained was to be applied to the human heart, a large mammalian heart, the dog's, was chosen for experiment. The method used depended upon electrographic registration of the exposed muscle's activity ; it consisted of accurate measurements of the rates of muscular conduction and of the refractory period in auricular muscle before and after administering quinidine in quantities comparable to those used clinically. The facts elicited and here relevant are that quinidine exerts a profound effect on the auricular muscle of the heart, lengthening its effective refractory period and slowing conduction through it. These observations were made as stated upon the dog's heart, but the validity of their application to man was rendered more probable by human electrocardiograms indicating that, as in the dog, conduction is depressed both in the ventricular and A-V muscle of man. Now evidence had previously been obtained, and is referred to

in Chapter 3, that auricular fibrillation results from a circus movement of the excitation wave in the auricle. If we suppose that the wave is so circulating in a ring of muscle such as that surrounding the mouth of the superior cava, then, at any given moment, a portion of this ring is in a state of activity and is

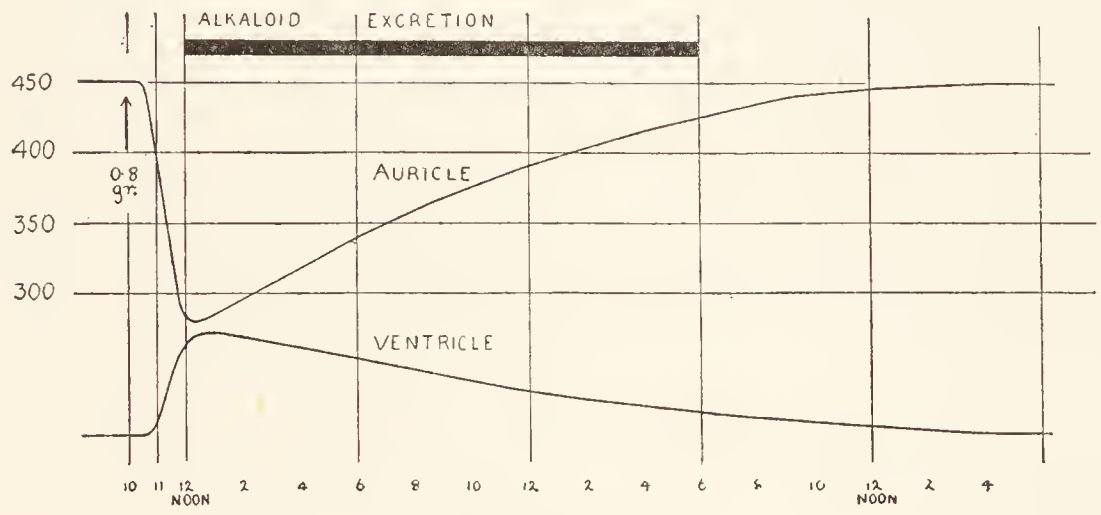


Fig. 48.

refractory (black in Fig. 49*a*). The wave is advancing through the ring at point *x* and the muscle is entering a state of quiescence or recovery at point *y*. The continued circulation of the wave

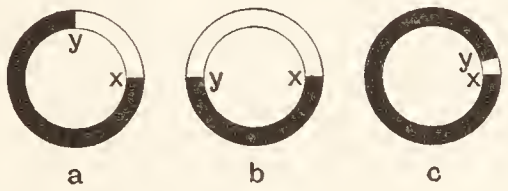


Fig. 49.

round and round the ring depends simply on the maintenance of a gap between the head of the wave and its tail. Now if the rate of conduction in the ring becomes slower, the wave will complete its circuit in a correspondingly longer time, and therefore will complete fewer revolutions per minute; but because the time for recovery from excitation is longer the gap between the head and tail of the circulating wave will tend to be increased, as indicated in Fig. 49*b*. On the other hand, if the refractory period lengthens, conduction rate remaining unaltered, the segment of muscle involved at any given moment will be longer and the gap will tend to be decreased as indicated in Fig. 49*c*. Supposing that the rate of conduction declines and the refractory period simultaneously increases, then, while the number of

revolutions a minute will decrease, change in the length of the gap will depend on the relative effects of the two factors involved, for these oppose each other. The gap may remain unchanged, it may narrow, or it may widen. If it narrows sufficiently it will close, and the wave will no longer continue to circulate. Thus quinidine, which conspicuously slows conduction and greatly lengthens the refractory period, theoretically may be expected to have one and perhaps two effects on a circus movement in the auricle. It should always diminish the number of circuits completed, slowing the auricular rate ; and, if its action on the effective refractory period sometimes outweighs its action on conduction, it will sometimes bring the movement to an end. The illustration given is a simpler one than the case of auricular fibrillation ; but the effects described are in fact the effects in auricular fibrillation also, and the description that has been given contains their accepted explanation.

*Digitalis and nitrites.* To show by further example the completeness with which observations upon man himself must govern the establishment of medicinal remedies, digitalis is named, than which there is no more valuable remedy in the pharmacopœa to-day. In 1785 Withering first showed us that foxglove will disperse dropsy, and in 1905-11 Mackenzie proved its most potent action to be its power of lowering ventricular rate in cases of what is now called auricular fibrillation. Between these two fundamental clinical discoveries was a leap in time, during which many pharmacological papers were published upon the action of digitalis and allied drugs on the amphibian and mammalian heart and blood vessels ; but these added almost nothing, directly or indirectly, to our understanding of digitalis as a remedy. Even the later knowledge that digitalis produces its therapeutic effects in auricular fibrillation by inducing heart block came from clinical sources. Pharmacology very naturally emphasised its discoveries of the drug's action on length of systole, strength of beat, and blood pressure; but these discoveries found during the period named no useful application, and their theoretical appeal was largely responsible for the almost indiscriminate administration of digitalis in heart cases, which was general at the end of last century, and for the drug being denied to cases of aortic regurgitation in which it may have high value ; in this is an instructive example of how unwisely theory may be allowed

precedence to immediately relevant experience. The most essential information, the profound effect which digitalis is capable of exerting in auricular fibrillation could not have been won through observation on the frog or normal mammal, but only as it was won, by observation on patients.

Nitrites first came to be used for anginal pain because venesection was known to relieve the pain and because nitrites, so it was thought, might similarly lower human blood pressure. Brunton's tests in patients proved that anginal pain may indeed be relieved by amyl nitrite, though we now know from clinical observations that the action is not due to lowered blood pressure, but is to be ascribed to dilatation of the coronary arteries ; and the same clinical observations, alluded to in Chapter 11, have explained why nitrites are so successful in some cases and fail so conspicuously in others. Consider the possibility of discovering other substances, equally potent or more potent remedially. Such work must now proceed on the basis laid down by clinical science, recognising in anginal pain a sensitive index of relative ischæmia of the cardiac muscle. Thus, pharmocology might discover substances powerfully dilating the coronary vessels ; but it could do no more than suggest that such a substance might prove serviceable in angina. Pharmacologists might measure the energy expenditure of the heart and the coronary flow in different circumstances, might conceivably correlate the two and show how this correlation would be affected by the new substance. It would be a difficult problem, the end result reached precariously and with infinite labour ; and this end result would apply to undiseased animals and not to a human being suffering from angina. The method of clinical science avoids all theoretical assumption, and the fallacies arising out of these, all error originating out of complex technique and artificial circumstance ; it brings us at once to the endpoint in a simple but crucial test in asking :—Does this substance in fact relieve anginal pain ? In its simple directness, and its capacity to produce the precisely relevant and easily intelligible answer, lie the virtues of this eminently scientific enquiry.

Note.—The work referred to in this chapter is more fully described in the following papers, from which other references can be obtained ; Grant, *Heart, Vol.* XVI, *p.* 318 ; Lewis, Drury, Iliescu and Wedd, *Heart, Vol.* IX, *p.* 54 and 207 ; Grant and Iliescu, *Ibid., p.* 289 ; Wayne, *Clinical Science, Vol.* 1, *p.* 63 ; Mackenzie, *Heart, Vol.* II, *p.* 273.